

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

REGISTRO DE PATENTES
Asesoramiento : 021 8691 11111111
Fecha : 11-11-2000 11:13:33
Página : 1 de 12
REGISTRO DE PATENTES
DIVISION DE NUEVAS CREACIONES

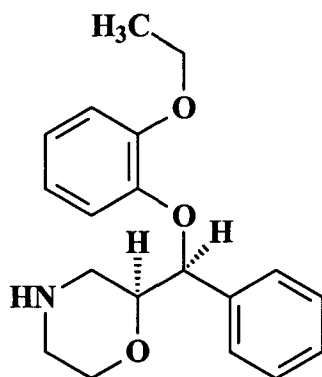
56

Re: P1.-PHARMACIA & UPJOHN COMPANY.-Solicitud de Patente e
Invención para "INHIBIDORES ALTAMENTE SELECTIVOS DE
LA RECAPTACION DE LA NOREPINEFRINA Y METODOS DE
USO DE LOS MISMOS".-Clase A.61.-Expediente número 00-
049.691.

1. Me refiero al auto dictado por ese Despacho notificado por Estado el 17 de Agosto de 2000 y a mi memorial de plazo de 26 de Septiembre del mismo año.

2. Anexas me permito presentar a usted:

- (1) Nuevas páginas 38 y 39 de las reivindicaciones, **que reemplazan las originalmente presentadas bajo los mismos números**, en las cuales se ha modificado la reivindicación 1, con el fin de reemplazar la expresión "...una composición que comprende un compuesto que tiene una selectividad farmacológica..." por la expresión "...una composición que comprende (S,S) reboxetina ópticamente pura o una sal farmacéuticamente aceptable de la misma, estando dicha reboxetina sustancialmente libre de su estereoisómero (R,R) y cuya fórmula estructural es:



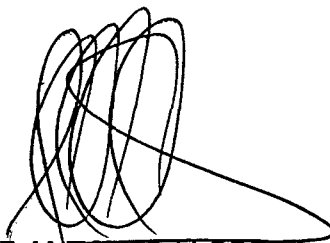
la cual tiene una selectividad farmacológica...". El sustento para dicha modificación se encuentra en las páginas 4, 5 y 12 de la descripción. Con dicha modificación se aclara al señor Examinador cual es el compuesto al que se hace referencia en la reivindicación 1 y cual es su fórmula estructural;

59

57

- (2) En original y dos copias, una de ellas de 6cm x 6cm, Arte Final de la fórmula química (II) característica del invento, para la publicación en la Gaceta de la Propiedad Industrial; y
- (3) Nuevo extracto en sus dos formas, **que reemplaza el originalmente presentado**, el cual incluye la reivindicación 1 que ha sido modificada.
3. Llamo su atención al hecho de que las copias debidamente certificadas de las primeras solicitudes presentadas para el invento arriba nombrado **respecto de las cuales reclamo prioridad**, a saber las solicitudes estadinenses números 60141968 de 1 de Julio de 1999, 60144131 de 16 de Julio de 1999, 60158256 de 6 de Octubre de 1999 y 60170381 de 13 de Diciembre de 1999, junto con las traducciones correspondientes a las partes pertinentes, fueron presentadas a ese Despacho mediante memorial de 2 de Octubre de 2000.
4. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



58

Expediente No		No de Folio
00049691		
Item	No de unidades	
1 CD		
2 DVD		
3 REVISTA		
4 LIBRO		
5 PERIODICO		
6 DISQUETES		
7 SOBRE DE MANILA *	1	✓
8 SOBRE BLANCO TAMAÑO CARTA		
9 SOBRE BLANCO TAMAÑO OFICIO		
10 OTROS:		

Observaciones:

CONTIENE ARTE FINAL

JOSE LLOREDA CAMACHO & CO.

ABOGADOS

CALLE 72 No. 5-83 - 5o. PISO

APARTADO AEREO 12304

TELEFAX: 212 6426 - 235 8846 - 346 1279 - 3458042

BOGOTA - COLOMBIA S.A.

PHARMACIA & UPJOHN COMPANY

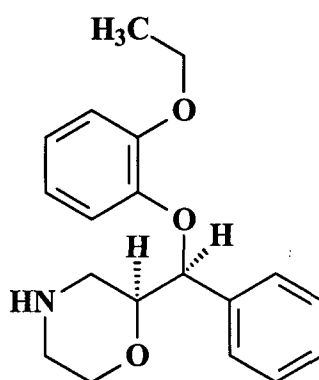
SOLICITUD DE PATENTE DE IVENCION

EXPEDIENTE No. 00-049.691

ARTE FINAL

REIVINDICACIONES

1. Una preparación de un medicamento a partir de una composición que comprende (S,S) reboxetina ópticamente pura o una sal farmacéuticamente aceptable de la misma, estando dicha reboxetina sustancialmente libre de su estereoisómero (R,R) y cuya fórmula estructural es:



la cual tiene una selectividad farmacológica de serotonina (K_i)/norepinefrina (K_i) de aproximadamente por lo menos 5 000 útil para tratar ó prevenir por lo menos una condición patológica del sistema nervioso seleccionada del grupo conformado por un desorden del tipo de adicción y síndrome de abstinencia, un desorden del tipo de desajustes, un desorden mental y de aprendizaje asociados con la edad, anorexia nerviosa, apatía, un desorden del tipo de déficit de atención causado por condiciones médicas generales, desorden de hiperactividad acompañado por déficit de atención, desorden bipolar, bulimia nerviosa, síndrome de fatiga crónica, estrés agudo o crónico, dolor crónico, desórdenes de la conducta, desorden ciclotímico, depresión, desorden distímico, fibromialgia y otros desórdenes somatoformes, desorden de ansiedad generalizada, incontinencia, un desorden por inhalación, un desorden por intoxicación, manía, cefaleas propias de la migraña, obesidad, desórdenes compulsivo-obsesivos y desórdenes de

espectro relacionado, desorden por desafío oposicional, desorden pánico, neuropatía periférica, desorden por estrés postraumático, desorden disfórico premenstrual, un desorden psicótico, desorden afectivo estacional, un desorden del sueño, fobia social, un desorden específico del crecimiento, síndrome de "poop out" (finalización prematura) de la inhibición selectiva de la recaptación de la serotonina (SSRI), y desórdenes del tipo de TICs.

2. Una preparación de un medicamento a partir de una composición que comprende reboxetina racémica útil para tratar ó prevenir por lo menos un desorden del sistema nervioso seleccionado del grupo conformado por un desorden del tipo de desajuste, un desorden mental y de aprendizaje asociado con la edad, anorexia nerviosa, apatía, un desorden del tipo de déficit de atención debido a condiciones médicas generales, desorden bipolar, bulimia nerviosa, síndrome de fatiga crónica, estrés agudo o crónico, dolor crónico, desorden ciclotímico, desorden distímico, fibromialgia y otros desórdenes somatoformes, incontinencia, manía, cefaleas causadas por migraña, obesidad, neuropatía periférica, desorden por estrés postraumático, desorden disfórico premenstrual, un desorden psicótico, desorden afectivo estacional, un desorden del sueño, desórdenes específicos del crecimiento, síndrome de "poop out" de la SSRI, y desórdenes del tipo de TICs.

61

República de Colombia



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL (E) DEL MINISTERIO DE
JUSTICIA Y DEL DERECHO

CERTIFICA:

Que por Resolución 541 del 27 de febrero de 1976, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas INGLÉS y ESPAÑOL al señor EDUARDO CALADO NOGUERA, identificado con la cédula de ciudadanía No. 17.177.588 expedida en Bogotá.

Que dicha Resolución se encuentra vigente en la fecha.

Se expide la presente certificación a solicitud del interesado.

Dada en Santa Fe de Bogotá, D.C., a

14 OCT. 1997

ALVARO NAMEN VARGAS

ICM/mmc
x
TR.

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 25 AGO. 1999
PABLO MENDEZ BARRAJAS

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 25 ABR. 2000
PABLO MENDEZ BARRAJAS

COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 26 NOV. 1997
COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 22 MAR. 2000
COMO NOTARIO SEXTO ENCARGADO
DE SANTA FE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA.
SANTA FE DE BOGOTA 19 JUN. 2000
PABLO MENDEZ BARRAJAS

REPUBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES

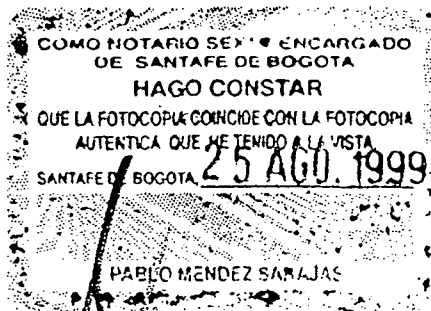
EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DEL MINISTERIO DE
RELACIONES EXTERIORES

CERTIFICA

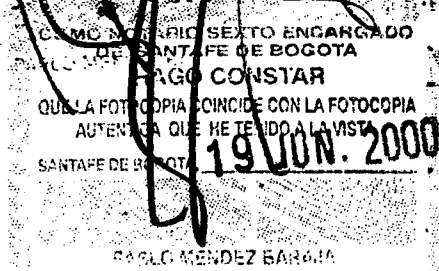
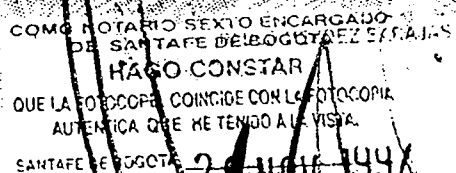
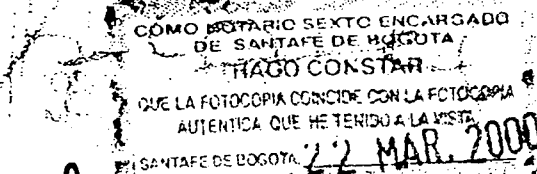
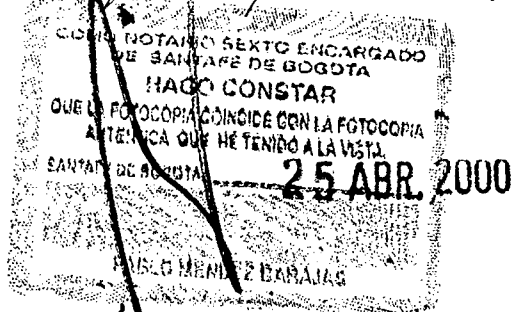
Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma del señor **EDUARDO CALADO NOGUERA**, como traductor e intérprete oficial para los Idiomas INGLES- ESPAÑOL, ESPAÑOL- INGLES, según resolución 541 del 27 de febrero de 1976.

La anterior certificación se expide a solicitud del interesado quien se identificó con cédula de ciudadanía 17.177.588 expedida en Bogotá.

Dada en Santa Fe de Bogotá, D.C., a los seis (6) de noviembre de 1997.



Blanca Acosta
BLANCA ACOSTA DE GARCIA
Jefe Area de Legalizaciones (e)



Junio 28, 2000
Traducción Oficial No.0281
REF:PHARMACIA & UPJOHN CO.
Patente No. 60/141,968

(Pharmacia & Upjohn)
Caso-28341/62484

63 66

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
OFICINA DE MARCAS Y PATENTES

Junio 06, 2000

Por medio del presente documento se certifica que adjunta se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud: 60/141,968

Fecha de Registro: Julio 01, 1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma:H. L. JACKSON

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes realzado de color dorado.

Eduardo Calzadilla

64

HOJA DE SOLICITUD PROVISIONAL
EN LA OFICINA DE MARCAS Y PATENTES DE LOS
ESTADOS UNIDOS

No de Caso: 28341/6248

TRAMITE PARA SOLICITUD PROVISIONAL DE PATENTE

Correo:
Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Estimados Señores:

Por medio de la presente solicitamos una Patente Provisional bajo el Código 37 de
Regulaciones Federales § 1.53 (c), de los siguientes inventores:

1. Erik H. F. Wong
7352 Hampstead Lane
Portage, Michigan
2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49 002
3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071

Eduardo Calacón
FOR OFFICIAL
USE ONLY

4. Robert MacArthur
531 Carrington Court
Kalamazoo, Michigan 49009

5. Duncan P. Taylor
8722 West F. Avenue
Kalamazoo, Michigan 49009

Titulo: METODOS PARA INHIBIR LA REASIMILACION DE LA NOREPINEFRINA

1. PARTES DE LA SOLICITUD INCLUIDAS

- 1 Título
- 25 Páginas de especificaciones (no incluyendo Reivindicaciones y resumen)
- 7 Páginas de reivindicaciones
- 1 Página resumen

CERTIFICADO DE CORREO POSTAL (37 CFR 1.10)

Yo, por medio del presente documento certifico que, el trámite provisional de patente y los documentos que hacen referencia a la misma, han sido enviados por Correo Certificado de Los Estados Unidos en la fecha de Julio 1, 1999, en un sobre rotulado al Comisionado Asistente para Patentes, Box Provisional Patent Application, Washington, DC., 20331. . mediante el Servicio de Correo Certificado al Destinatario del Servicio Postal de los Estados Unidos, bajo el envío número EM362732485US.

Firma: Enviado por: Richard Zimmermann

Documentos adicionales Adjuntos

Eduardo Calado
DIRECTOR OF PATENT
INVESTIGATION
JUL 1 1999

89
66

- ☐ Certificado de Deposito Biológico
 - ☐ Un disco que contiene nucleotidos y/o secuencia de amino ácidos en formato legible por computadora.
 - ☐ Programa de Computadora Microficha
 - ☐ Declaraciones verificadas de reivindicaciones de estatus de Pequeña empresa bajo el Código de Regulaciones Federales 1.9 y 1.27
 - ☐ Poder
 - ☐ Traducción Oficial de solicitudes de patente en otro idioma aparte del inglés.
 - ☐ Transferencia del Invento
 - ☒ Sobre con timbre prepago
 - ☐ Otros Honorarios (ej. copia juramentada)

3. Cálculo de Registro Honorarios (37 CFR 1.16)

- ☒ Solicitud provisional (\$75.00/\$150.00 Honorarios registro : \$150.00
- ☐ Otros Honorarios (ej. Registro de Traspaso) Honorarios registro: _____
- Total de Honorarios adjuntos \$150.00

4. Forma de Pago de Honorarios

- ☐ Se adjunta cheque de la Empresa por la suma de: \$150.00
- ☐ Cobrar a Cuenta Corriente No. 13.2855 por la suma de: _____

Se anexa una copia de este Trámite

- ☐ No se anexa copia de trámite

5. Por medio de la presente el Comisionado está autorizado para cobrar deficiencias en el monto adjunto o cualquier honorario adicional que se requiera durante la vigencia de esta solicitud bajo el Código de Regulaciones Federales 37 §1.16 o Código de Regulaciones

Eduardo Calzadilla
Eduardo Calzadilla
"TRAMITADOR OFICIAL"
SECRETARÍA DE ECONOMÍA
MEXICO

40
67

Federales 37 §1.17 o bajo cualquier otra regulación aplicable (a excepción del pago de los Honorarios por emisión) a la Cuenta Corriente No. 13.2855. Se adjunta una copia de este trámite.

Favor reembolsar cualquier sobrepago a: Marshall, O'Toole, Gersnstein, Murray & Borum a la dirección a continuación:

Favor dirigir todas las llamadas a : James Napoli a la siguiente dirección:

Atentamente,

MARSHALL, OTOOLE, GERNSTEIN, MURRAY & BORUN

6300 Sears Tower

233 South Wacker Drive

Chicago, Illinois 60606-6402

Tel: (312) 474-6300

Edwards Calabrese
EDWARDS CALABRESE
ATTORNEYS AT LAW
CHICAGO, ILLINOIS
312.474.6300

COINVENTORES

Expediente No. 28341/6248

CERTIFICADO DE CORREO POSTAL

Servicio Postal, CORREO INMEDIATO, bajo el envío número EM362732485US.

Yo, por medio del presente documento certifico que este documento (u honorarios), han sido enviados por Correo Certificado de Los Estados Unidos "CORREO POSTAL INMEDIATO AL DESTINATARIO" bajo el código 37 Código de Regulaciones Federales §1.10 en la fecha indicada anteriormente y rotulado a: Box Provisional Patent Application, Assistant Commissioner for patents, Washington, D.C.20231

Richard Zimmermann

SOLICITUD PROVISIONAL PARA CARTAS DE PATENTES
DE LOS ESTADOS UNIDOS

ESPECIFICACION

A todos aquellos a quien pueda interesar:

Se informa que nosotros, Erik H. F. Wong, ciudadano de los Estados Unidos de América, residente en 7352 Hampstead lane, portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, ciudadano de los Estados Unidos de América, residente en 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall, un ciudadano del Reino Unido, residente en 7560 Fieldwood Circle, Mattawan, Michigan,

Edwardo Calabaz...

49071, Van Buren County; Robert MacArthur, ciudadano del Reino Unido y Canadá, residente En 531 Carrington Court, Kalamazoo, Michigan, 49009, Kalamazoo County; y Duncan P. Taylor, ciudadano de los Estados Unidos de America, residente en 8722 West F. Avenue, Kalamazoo, Michigan, 49009, Kalamazoo County, son autores del invento original e útil, llamado "METODOS PARA INHIBIR LA REASIMILACION DE LA NOREPINEFRINA", sobre la cual la siguiente es una especificación:

Abogados solicitantes:

James J. Napoli (No Reg. 32, 361

Marshall, O'Toole, Gerstein, Murray & Borum

6300 Sears Tower

233 South Wacker Drive

Chicago, Illinois 60606-6402

EdUARdo Calado N.
"IRADU 1020"
R.C.
Rev 54

REIVINDICACIONES:

1. Un método para tratar el sufrimiento humano de una condición, en el cual los inhibidores de norepinefrina proporcionan un beneficio. El método consiste en el suministro de una cantidad terapéuticamente eficaz de una reboxetina ópticamente pura (S,S), o una sal farmacéuticamente aceptable de la misma, a dicha reboxetina individual ópticamente pura (S, S) siendo esta substancialmente libre de reboxetina (R, R).

2. Un método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.1 hasta alrededor de 10 mg/día.

3. El método de acuerdo a la reivindicación 2 en el cual dicha reboxetina (S, S) se suministra aproximadamente 0.5 hasta alrededor de 8 mg/día.

4. El método de acuerdo a la Reivindicación 3 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 5mg/día.

Edvarcho Calado

5. El método de acuerdo a la Reivindicación 4 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 2.5 mg/día.

6. El método de acuerdo a la Reivindicación 5 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.9 mg/día.

7. El método de acuerdo a la Reivindicación 6 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.8 mg/día.

8. El método de acuerdo a la Reivindicación 7 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.75 mg/día.

9. El método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra por vía oral, parenteral, transdermico, rectal o vaginal.

Edwards Caladot

72

10. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra oralmente con un portador farmacéuticamente aceptable el cual consta de por lo menos una substancia aglutinante, diluyente, lubricante, agente desintegrante, agente efervescente, materia colorante, dulcificante y agente húmedo.

11. El método de acuerdo a la reivindicación 10 en el cual el suministro oral es mediante un sachet, cápsula, tableta o aerosol.

12. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra parenteralmente subcutánea, intravenosa o intramuscular.

13. El método de acuerdo a la Reivindicación 1, en la cual la sal farmacéuticamente aceptable es metanosulfonado.

14. El método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) o sal farmacéuticamente aceptable del mismo, consiste de aproximadamente 90% de peso de la reboxetina (S,S) o inferior de alrededor 10% del peso de la reboxetina (S, S) basado en el peso total de la reboxetina presente.

Edwards Calado

15. El método de acuerdo a la Reivindicación 14 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, consiste de aproximadamente por lo menos 97% del peso de reboxetina (S, S) e inferior de alrededor de 3 % del peso de la Reboxetina (S, S), basado en el peso total de la reboxetina presente.

16. El método de acuerdo a la Reivindicación 15 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, consiste de aproximadamente por lo menos 99% del peso de reboxetina (S, S) e inferior de alrededor de 1 % del peso de la Reboxetina (S, S), basado en el peso total de la reboxetina presente.

17. El método de acuerdo a la reivindicación 1 en el cual dicha condición es de por lo menos un trastorno adictivo y síndrome de abstinencia, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno de conducta, trastorno ciclotimia, depresión, trastorno distímico, fibromialgia y otros trastornos somáticos, trastorno de ansiedad generalizada, trastornos de inhalación,

Edvarado Calado

74

trastornos de intoxicación, obesidad, trastorno obsesivo -compulsivo y trastornos relacionados con el espectro, trastorno de desafío de oposición, trastorno de pánico, neuropatía periférica, trastorno de estrés post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno afectivo temporal, trastorno del sueño, fobia social, trastorno de desarrollo específico y inhibidores de serotonina selectiva (SSRI), síndrome de defecarse.

18. El método de acuerdo a la reivindicación 17 en la cual los trastornos adictivos consisten de una adicción de por lo menos un alcohol, nicotina y otras sustancias psicoactivas.

19. El método de acuerdo a la reivindicación 17 en la cual los trastornos de acoplamiento constan de estado de ánimo depresivo, ansiedad, ansiedad mezclada y ánimo depresivo, alteración en la conducta y alteraciones en la conducta mezcladas con el estado de ánimo.

20. El método de acuerdo a la reivindicación 17 en la cual los trastornos de aprendizaje relacionados con la edad y trastornos mentales consiste del mal de Alzheimer's.

Edwards Calabrese

21. El método de acuerdo a la reivindicación 17 en la cual la depresión consiste de depresión adolescente o depresión menor.

22. El método de acuerdo a la reivindicación 17 en la cual el trastorno disfórico premenstrual consiste del síndrome premenstrual y trastorno disfórico en fase tardía **luctal**.

23. El método de acuerdo a la reivindicación 17 en la cual el trastorno sicótico cosiste de esquizofrenia, esquizoactivo y trastorno sicoafectivo.

24. El método de acuerdo a la reivindicación 17 en la cual la fobia social consiste de trastorno de ansiedad social.

25. El método de acuerdo a la reivindicación 17 en la cual el trastorno del sueño consiste de narcolepsia y enuresis.

26. El método de acuerdo a la reivindicación 17 en la cual el trastorno somático consiste de trastornos de somatización, trastorno de conversión, trastorno de dolor, hipocondría, trastorno de dismorfia corpórea, trastorno no identificado somático y somatoformas NOS.

Eduardo Calacash

27. El método de acuerdo a la reivindicación 17 en el cual dicha condición es de por lo menos un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, depresión, trastorno distímico, trastorno de ansiedad generalizada (GAD), adicción a la nicotina, trastorno de estrés post-traumático, trastorno disfórico premenstrual, trastorno sicótico, y (SSRI), síndrome de defecarse.

28. El método de acuerdo a la reivindicación 27 en el cual dicha condición es por lo menos una de apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, síndrome de fatiga crónica, trastorno ciclotímico, depresión, adicción a la nicotina, trastorno de stress post-traumático, y (SSRI), síndrome de defecarse.

29. Un método para tratar un sufrimiento debido a una condición en el cual los inhibidores de norepinefrina proporcionan un beneficio, mientras que disminuye los efectos secundarios, el método consiste en suministrar una dosis total aproximada de 0.1 hasta alrededor de 10mg/día de una

Edwardo Calado

reboxetina. (S, S) ópticamente pura o una sal farmacéuticamente aceptable del mismo, a un individuo, siendo dicha reboxetina (S, S) ópticamente pura y substancialmente libre de (R,R) reboxetina.

30. El método de acuerdo a la reivindicación 29 en la cual dichos efectos adversos consisten de mareos, insomnio, atolondrado, cambios en presión sanguínea, sudores, trastornos intestinales, disfunción sexual en hombres, efectos parecidos a anticolinérgicos, y efectos secundarios con interacción de drogas.

31. Un método para el tratamiento de trastornos del sistema nervioso, el cual consiste en los siguientes pasos: el suministro de una dosis terapéuticamente eficaz de reboxetina racémica o una sal farmacéuticamente aceptable del mismo a un individuo que necesite dicho tratamiento, en el cual dicho trastorno es por lo menos uno de los trastornos de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno

Edward Calas H.

disfórico premenstrual, trastorno sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno de desarrollo específico, y (SSRI), síndrome de defecarse.

32. El método de acuerdo a la reivindicación 31 en el cual el trastorno es de por lo menos uno de los trastornos de acoplamiento, trastorno de déficit de aprendizaje debido a la edad, o trastorno mental, apatía, bulimia nervosa, fatiga crónica, trastorno ciclotímico, trastorno distímico, trastorno de estrés post traumático, trastorno disfórico premenstrual, trastorno sicótico, y (SSRI) síndrome de defecarse .

33. El método de acuerdo a la reivindicación 32, en el cual dicho trastorno es por lo menos uno relacionado con la apatía, fatiga crónica, trastorno ciclotímico, trastorno de estrés post traumático y SSRI síndrome de defecarse.

34. El método de acuerdo a la reivindicación 31, en el cual la reboxetina se suministra al individuo en una cantidad aproximada de 2 hasta 20 mg/día.

Eduardo Calabro

87
79

35. El método de acuerdo a la reivindicación 34, en el cual la reboxetina se suministra en una cantidad aproximadamente de 4 hasta 10 mg/día.
36. El método de acuerdo a la reivindicación 35, en la cual la reboxetina se suministra aproximadamente de 6 hasta 10 mg/día.
37. El método de acuerdo a la reivindicación 31, en el cual dicha reboxetina se suministra por vía oral, parenteral, transdermica, rectal o vaginal.
38. El método de acuerdo a la reivindicación 37, en la cual dicha reboxetina se suministra oralmente con un portador farmacéuticamente aceptable, el cual consta de por lo menos un menos una sustancia aglutinante, diluyente, lubricante, agente desintegrante, agente efervescente, materia colorante, dulcificante y agente húmedo.
39. El método de acuerdo a la reivindicación 10 en el cual el suministro oral es mediante un sachet, cápsula, tableta o aerosol.

Eduardo Calas

40. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra parenteralmente subcutánea, intravenosa o intramuscular.
41. El método de acuerdo a la Reivindicación 1, en la cual la sal farmacéuticamente aceptable es metanosulfonado.
42. Una preparación de un medicamento de una composición que consta de reboxetina para tratar por lo menos un trastorno del sistema nervioso seleccionado del grupo que consiste de trastorno de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad y trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno de desarrollo específico, y (SSRI), síndrome de defecarse.
43. El uso de la reboxetina para la fabricación de un medicamento para tratar por lo menos un trastorno del sistema nervioso

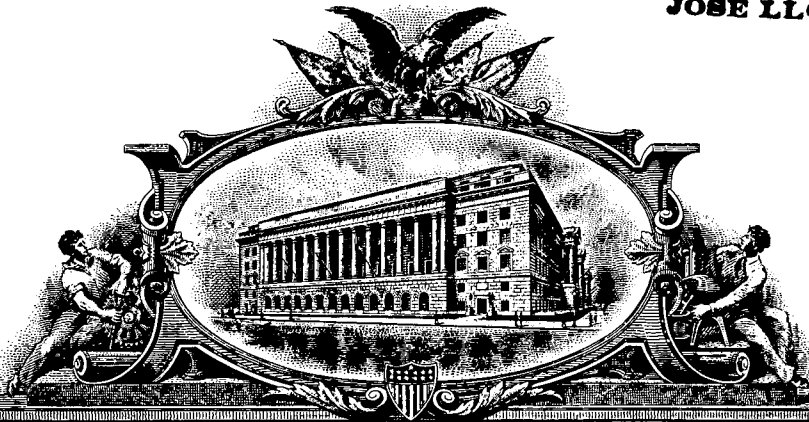
Edwards Calado 12

81

seleccionado de un grupo que consiste de trastornos de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad y trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno de desarrollo específico, y (SSRI), síndrome de defecarse.

Eduardo Calado

PA 258501



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 06, 2000

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 60/141,968

FILING DATE: July 01, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

**H. L. JACKSON
Certifying Officer**

66/10/10
1c553 U.S. PTO
07/01/99

12/1/99
88

PROVISIONAL PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No: 28341/6248

PROVISIONAL PATENT APPLICATION TRANSMITTAL

**Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231**

1c541 U.S. PTO
60/141968
07/01/99

Sir:

Transmitted herewith for filing is the provisional patent application under 37 CFR 1.53(c) of

Inventors:

- | | |
|---|--|
| 1. Erik H.F. Wong,
7352 Hampstead Lane
Portage, Michigan 49024 | 4. Robert MacArthur
531 Carrington Court
Kalamazoo, Michigan 49009 |
| 2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49002 | 5. Duncan P. Taylor
8722 West F Avenue
Kalamazoo, Michigan 49009 |
| 3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071 | |

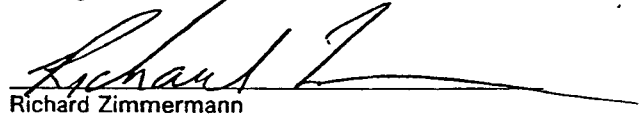
Title: METHODS FOR INHIBITING REUPTAKE OF NOREPINEPHRINE

1. Application Papers Enclosed

- | | |
|----|--|
| 1 | Title Page |
| 25 | Pages of Specification (excluding Claims & Abstract) |
| 7 | Pages of Claims |
| 1 | Page of Abstract |

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Provisional Patent Application Transmittal and the documents referred to as enclosed therewith are being deposited with the United States Postal Service on July 1, 1999, in an envelope addressed to the Assistant Commissioner for Patents, Box Provisional Patent Application, Washington, D.C. 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing Label No. EM362732485US.


Richard Zimmermann

66/10/10-88888888

81
84

2. Additional Papers Enclosed

- ☐ Declaration of Biological Deposit
- ☐ Computer readable copy of sequence listing containing nucleotide and/or amino acid sequence
- ☐ Microfiche computer program
- ☐ Verified statement(s) claiming small entity status under 37 CFR 1.9 and 1.27
- ☐ Associate power of attorney
- ☐ Verified translation of a non-English patent application
- ☐ An assignment of the invention
- ☒ Return Receipt Postcard
- ☐ Other (e.g. declaration or oath)

3. Filing Fee Calculation (37 CFR 1.16)

- | | | |
|--|-------------|-----------------|
| ☒ Provisional Application (\$75.00/\$150.00) | Filing Fee: | \$150.00 |
| ☐ Other Fees (e.g. Recording Assignment) | Filing Fee: | \$_____ |
| Total Fees Enclosed | | \$150.00 |

4. Method of Payment of Fees

- ☒ Enclosed is our firm check in the amount of: \$150.00
- ☐ Charge Deposit Account No. 13-2855 in the amount of: \$_____
A copy of this Transmittal is enclosed.
- ☐ Not enclosed

5. Deposit Account and Refund Authorization

The Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees which may be required during the pendency of this application under 37 CFR 1.16 or 37 CFR 1.17 or under other applicable rules (except payment of issue fees), to Deposit Account No. 13-2855. A copy of this Transmittal is enclosed.

Please refund any overpayment to Marshall, O'Toole, Gerstein, Murray & Borun at the address below.

667020-8967409

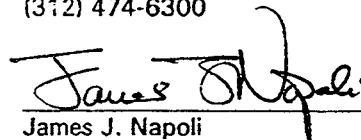
88
85

Please direct all future communications to James J. Napoli, at the address below.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

By:



James J. Napoli
Reg. No: 32,361

July 1, 1999

60606-6402

JOINT INVENTORS

Attorney Docket No. 28341/6248

"EXPRESS MAIL" mailing label No. EM362732485US.

Date of Deposit: July 1, 1999

I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D. C. 20231

Richard Zimmermann

**PROVISIONAL APPLICATION FOR
UNITED STATES LETTERS PATENT
SPECIFICATION**

TO ALL WHOM IT MAY CONCERN:

Be it known that we, Erik H.F. Wong, a citizen of the United States of America, residing at 7352 Hampstead Lane, Portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, a citizen of the United States of America, residing at 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall, a citizen of the United Kingdom, residing at 7560 Fieldwood Circle, Mattawan, Michigan, 49071, Van Buren County; Robert MacArthur, a citizen of the United Kingdom and Canada, residing at 531 Carrington Court, Kalamazoo, Michigan, 49009, Kalamazoo County; and Duncan P. Taylor, a citizen of the United States of America, residing at 8722 West F Avenue, Kalamazoo, Michigan, 49009, Kalamazoo County, have invented new and useful "METHODS FOR INHIBITING REUPTAKE OF NOREPINEPHRINE," of which the following is a specification.

Attorneys for Applicants:

**James J. Napoli (Reg. No. 32,361)
Marshall, O'Toole, Gerstein,
Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402**

90
87

METHODS FOR INHIBITING REUPTAKE OF NOREPINEPHRINE

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods of treating individuals suffering from a variety of conditions wherein inhibiting reuptake of norepinephrine provides a benefit. In particular, the present invention relates to methods of treatment comprising administration of reboxetine to an individual to selectively inhibit the reuptake of norepinephrine.

Brief Description of Related Technology

Many types of depression, mental, behavioral, and neurological disorders originate from disturbances in brain circuits that convey signals using certain monoamine neurotransmitters. Monoamine neurotransmitters include, for example, norepinephrine (noradrenaline), serotonin (5-HT), and dopamine. Lower-than-normal levels of norepinephrine are associated with a variety of symptoms including lack of energy, motivation, and interest in life. Thus, a normal level of norepinephrine is essential to maintaining drive and capacity for reward.

These neurotransmitters travel from the terminal of a neuron across a small gap (*i.e.*, the synaptic cleft) and bind to receptor molecules on

60144958 070199

the surface of a second neuron. This binding elicits intracellular changes that initiate or activate a response or change in the postsynaptic neuron.

Inactivation occurs primarily by transport (*i.e.*, reuptake) of the neurotransmitter back into the presynaptic neuron. Abnormality in noradrenergic transmission results in various types of depression, mental, behavioral, and neurological disorders attributed to a variety of symptoms including a lack of energy, motivation, and interest in life. *See generally*, R.J. Baldessarini, "Drugs and the Treatment of Psychiatric Disorders: Depression and Mania" in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, NY, NY, pp. 432-439 (1996).

Reboxetine (*i.e.*, 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine) raises the concentration of physiologically active norepinephrine by preventing reuptake of norepinephrine, for example. Reboxetine is a norepinephrine reuptake inhibitor and has been shown to be effective in the short-term (*i.e.*, less than eight weeks) and long-term treatment of depression. In fact, reboxetine has been shown to have effectiveness that is similar to fluoxetine, imipramine, and desipramine, commonly prescribed antidepressants, in both adults and elderly patients. *See* S.A. Montgomery, *Reboxetine: Additional Benefits to the Depressed Patient*, *Psychopharmacol (Oxf)* 11:4 Suppl., S9-15 (Abstract) (1997).

Antidepressant drugs are sometimes divided into "generations." The first generation included the monoamine oxidase inhibitors (such as isocarboxazid and phenylhydrazine) and tricyclic agents (such as imipramine). The second generation of antidepressant drugs included compounds such as mianserin and trazodone. The third generation has included drugs called selective reuptake inhibitors (*e.g.*, fluoxetine, sertraline, paroxetine, and reboxetine). Those drugs were characterized by relatively selective action on only one of the three main monoamine systems thought to be involved in depression (*i.e.*, 5-HT (serotonin), noradrenaline (norepinephrine), and dopamine). *APP Textbook of Psychopharmacology* (A.F. Schatzberg and C.B.

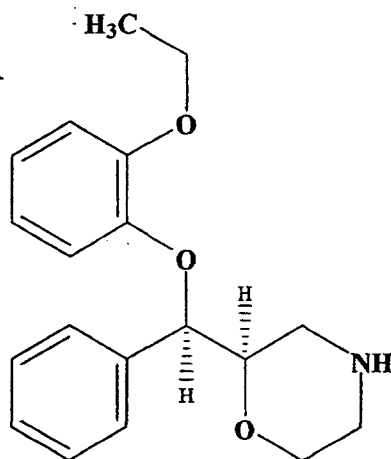
Q2
87

5 Nemeroff), American Psychiatric Press, 2d. ed., (1998); Lexicon of Psychiatry,
Nuerology and the Neurosciences (F.J. Ayd, Jr.) Williams and Wilkins (1995).
The antidepressant efficacy of reboxetine is evidenced by its ability to prevent
reserpine-induced blepharospasm and hypothermia in mice, down regulation of
β-adrenergic receptors and desensitization of noradrenaline-coupled adenylate
cyclase. See M. Brunello and G. Racagni, "Rationale for the Development of
Noradrenaline Reuptake Inhibitors," Human Psychopharmacology, vol. 13, S-
13-519, Supp. 13-519 (1998).

10 Reboxetine generally is described in Melloni *et al.* U.S. Patent
Nos. 4,229,449, 5,068,433, and 5,391,735, and in GB 2,167,407, the
disclosures of which are hereby incorporated by reference. Chemically,
reboxetine has two chiral centers and, therefore, exists as two enantiomeric
pairs of diastereomers, shown below as isomers (I) through (IV):

(I)

15

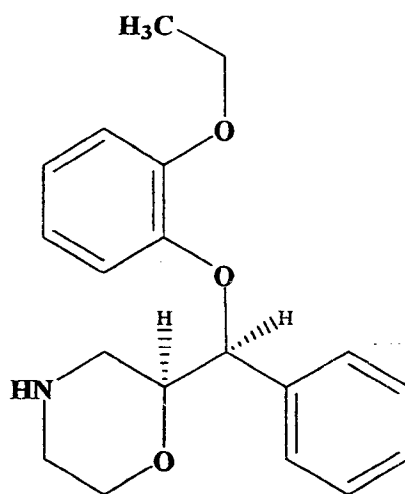


20

(R, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

20
70

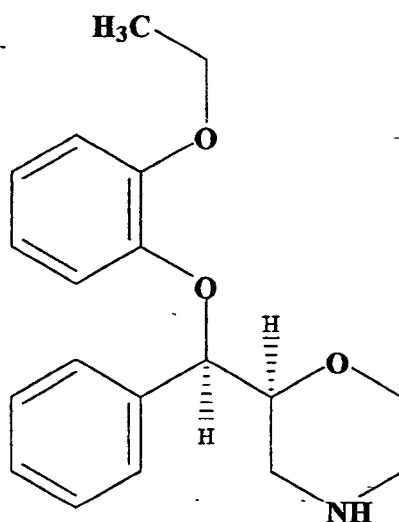
(II)



(S, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

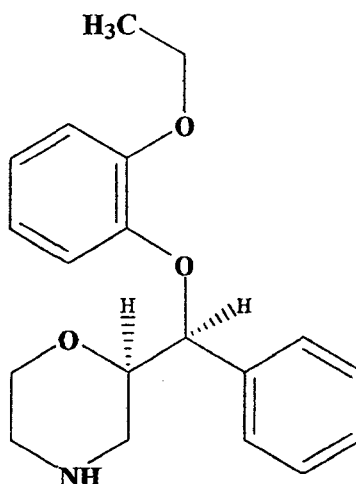
10

(III)



(R, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

(IV)



(S, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes D and L, or (+) or (-), designate the sign of rotation of plane-polarized light by the compound, with L or (-) meaning that the compound is levorotatory. In contrast, a compound prefixed with D or (+) is dextrorotatory. There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. Thus, D-lactic acid is the same as (-)-lactic acid, and L-lactic acid is the same as (+)-lactic acid. For a given chemical structure, each of a pair of enantiomers are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric, or racemic, mixture.

Stereochemical purity is important in the pharmaceutical field, where many of the most often prescribed drugs exhibit chirality. For example, the L-enantiomer of the beta-adrenergic blocking agent, propranolol, is known

to be 100 times more potent than its D-enantiomer. Additionally, optical purity is important in the pharmaceutical drug field because certain isomers have been found to impart a deleterious effect, rather than an advantageous or inert effect. For example, it is believed that the D-enantiomer of thalidomide is a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, whereas its corresponding L-enantiomer is believed to be a potent teratogen.

When two chiral centers exist in one molecule, there are four possible stereoisomers: (R,R), (S,S), (R,S), and (S,R). Of these, (R,R) and (S,S) are an example of a pair of enantiomers (mirror images of each other), which typically share chemical properties and melting points just like any other enantiomeric pair. The mirror images of (R,R) and (S,S) are not, however, superimposable on (R,S) and (S,R). This relationship is called diastereoisomeric, and the (S,S) molecule is a diastereoisomer of the (R,S) molecule, whereas the (R,R) molecule is a diastereoisomer of the (S,R) molecule.

Currently, reboxetine is commercially available only as a racemic mixture of enantiomers, (R,R) and (S,S) in a 1:1 ratio, and reference herein to the generic name "reboxetine" refers to this enantiomeric, or racemic, mixture. Reboxetine is commercially sold under the trade names of EDRONAX™, PROLIFT™, VESTRA™, and NOREBOX™. As previously noted, reboxetine has been shown to be useful in the treatment of human depression. Orally administered reboxetine is readily absorbed and requires once or twice a day administration. A preferred adult daily dose is in the range of about 8 to about 10 milligrams (mg). The effective daily dosage of reboxetine for a child is smaller, typically in a range of about 4 to about 5 mg. The optimum daily dosage for each patient, however, must be determined by a treating physician taking into account the patient's size, other medications which the patient may be taking, identity and severity of the particular disorder, and all of the other circumstances of the patient.

Administration of reboxetine, however, can result in undesired side effects associated with drug-drug interactions and in other undesirable effects such as, for example, dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in males, certain anticholinergic-like effects (e.g., tachyarrhythmia and urinary retention), and undesired side effects associated with drug-drug interactions.

Accordingly, there is a need in the art for a method of treating individuals suffering from a variety of conditions where inhibiting reuptake of norepinephrine provides a benefit, while reducing or eliminating the adverse side effects associated with conventional norepinephrine reuptake inhibitors. There also is a need for a method that selectively inhibits the reuptake of norepinephrine over other neurotransmitters, like serotonin and dopamine.

SUMMARY OF THE INVENTION

The present invention generally is directed to methods of treating a variety of conditions where inhibition of norepinephrine reuptake provides a benefit. More particularly, the present invention is directed to an effective treatment of such conditions comprising administration of reboxetine, or an optically pure (S,S) stereoisomer thereof, to a human. Individuals treated with optically pure (S,S) reboxetine do not experience certain adverse side effects associated with the administration of the racemic mixture of (R,R) and (S,S) reboxetine. The present invention therefore includes administering optically pure (S,S) reboxetine to a human to selectively inhibit norepinephrine reuptake, and thereby control, reduce, or eliminate adverse effects caused by the administration of the racemic mixture of reboxetine.

More specifically, one embodiment of the present invention is directed to a method of treating a human condition wherein inhibiting reuptake of norepinephrine provides a benefit. The method comprises the step of administering a therapeutic amount, typically about 0.5 to about 10 mg/day, of

91
94

optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof.
Optically pure (S,S) reboxetine is substantially free of (R,R) reboxetine.

Human conditions that can be treated by inhibiting the reuptake of norepinephrine include, but are not limited to, addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances) and withdrawal syndrome, adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, depression (including adolescent depression and minor depression), dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder (GAD), inhalation disorders, intoxication disorders (alcohol addiction), obesity (*i.e.*, reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response).

Optically pure (S,S) reboxetine is advantageous over prior treatment methods which utilized a racemic mixture of (R,R) and (S,S)

reboxetine. In particular, it has been found that treatments using compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers.

5 Therefore, reuptake blockage can be achieved with much lower dosages. Accordingly, the present invention may permit a substantial reduction in the customary daily dosage of the racemic mixture (*i.e.*, the commercially available reboxetine) by about 50% to about 80% because of the use of an optically pure (S,S) reboxetine. In addition, treatments utilizing the optically pure (S,S)
10 reboxetine may result in fewer undesirable adverse side effects associated with the treatment because of the high selectivity and potency of (S,S) reboxetine with respect to inhibiting the reuptake of norepinephrine.

Another embodiment of the present invention is directed to a method of treating a nervous system disorder comprising the step of
15 administering a therapeutically effective dose of racemic reboxetine to an individual, wherein the disorder is at least one of adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease),
20 anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated
25 somatoform disorder, and somatoform NOS), obesity (*i.e.*, reducing the weight of obese or overweight patients), peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luctal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizopreniform disorders), seasonal affective disorder,
30 sleep disorders (such as narcolepsy and enuresis), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out"

0014968-070109

99
95

syndrome. Other embodiments of the present invention are directed to a preparation of a medicament from a composition comprising reboxetine and a use of reboxetine in a manufacture of the medicament to treat at least one of the aforementioned nervous system disorders.

5 Additional benefits and features of the present invention will become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the example and the appended claims. It should be noted, however, that while the invention is susceptible of
10 embodiments in various forms, described hereafter are specific preferred embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 Reboxetine is a known compound that is active on the central nervous system. Reboxetine has been used as an antidepressant, and has been suggested for the treatment of oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder. These proposed treatments are disclosed in International Publication Nos. WO 99/15163, WO
20 95/15176, and WO 99/15177.

Heretofore, use of reboxetine has been limited to the treatment of depression, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder. Furthermore, prior treatment methods using reboxetine administered a racemic mixture of the (S,S) and (R,R)
25 stereoisomers. One embodiment of the present invention, however, is directed to an effective method using an optically pure (S,S) stereoisomer of reboxetine to treat conditions wherein inhibition of reuptake of norepinephrine is beneficial. (S,S) Reboxetine is an effective, selective inhibitor of norepinephrine reuptake and, accordingly, dose levels can be substantially

reduced in comparison to racemic reboxetine. In addition, individuals treated with an optically pure (S,S) reboxetine do not experience certain adverse effects associated with the administration of the racemic mixture of (R,R) and (S,S) reboxetine. Accordingly, one embodiment of the present invention
5 includes administering a therapeutic amount of an optically pure (S,S) reboxetine to a human to inhibit the reuptake of norepinephrine, and to control, reduce, or eliminate adverse effects associated with administration of racemic reboxetine.

More specifically, one embodiment of the present invention is
10 directed to a method of treating a human condition wherein inhibiting reuptake of norepinephrine provides a benefit. The method comprises the step of administering, and preferably orally administering, a total dose of about 0.5 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual. The optically pure (S,S) reboxetine is
15 substantially free of (R,R) reboxetine.

As used herein, the term "reboxetine" refers to the racemic mixture of the (R,R)- and (S,S) enantiomers of reboxetine. In contrast, the term "(S,S) reboxetine" refers to only the (S,S) stereoisomer. Similarly, the term "(R,R) reboxetine" refers to only the (R,R) stereoisomer.

20 The phrases "optically pure (S,S) reboxetine" and "substantially free of its (R,R) stereoisomer," as used herein, mean that the composition contains a greater proportion of (S,S) reboxetine in relation to (R,R) reboxetine. In a preferred embodiment, the phrases mean that the composition is at least 90 percent by weight (wt.%) of (S,S) reboxetine, and 10 wt.% or less
25 of (R,R) reboxetine. In a more preferred embodiment the phrases mean that the composition contains at least 97 wt.% of (S,S) reboxetine, and 3 wt.% or less of (R,R) reboxetine. In an even more preferred embodiment, the phrases mean that the composition contains at least 99 wt.% of (S,S) reboxetine, and 1 wt.% or less of (R,R) reboxetine. In a most preferred embodiment, the phrases
30 "optically pure (S,S) reboxetine" and "substantially free of its (R,R)

3 (a)

stereoisomer," as used herein, mean that the composition contains greater than 99 wt.% of (S,S) reboxetine. The foregoing percentages are based upon the total amount of reboxetine present in the composition. The phrases "substantially free of (R,R) reboxetine," "substantially optically pure (S,S) stereoisomer of reboxetine," "substantially optically pure (S,S) reboxetine," "optically pure (S,S) stereoisomer of reboxetine," and "optically pure (S,S) reboxetine" are also encompassed by the above-described amounts.

The phrases "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases. Because the active compound (*i.e.*, (S,S) reboxetine) used in the present invention is basic, salts may be prepared from pharmaceutically acceptable acids. Suitable pharmaceutically acceptable acids include acetic, benzenesulfonic (besylate), benzoic, p-bromophenylsulfonic, camphorsulfonic, carbonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, isethionic, lactic, maleic, malic, mandelic, methanesulfonic (mesylate), mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. Examples of such pharmaceutically acceptable salts of (S,S) reboxetine, thus, include, but are not limited to, acetate, benzoate, β -hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, and the like. A preferred pharmaceutical salt of (S,S) reboxetine is methanesulfonate (*i.e.*, mesylate), which is prepared using methanesulfonic acid.

5 The phrases "adverse effects" and "adverse side effects" in relation to reboxetine include, but are not limited to, dizziness, insomnia, lightheadedness, changes in blood pressure, gastrointestinal disturbances, sexual dysfunction in males, extrapyramidal side effects, certain anticholinergic-like effects (*e.g.*, tachycardia, blurred vision), and undesired side effects associated with with drug-drug interactions.

10 More specifically, administration of an optically pure (S,S) reboxetine is effective in treating various human conditions including, but not limited to, addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances) and withdrawal syndrome, adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to
 15 general medical conditions, attention-deficit hyperactivity disorder (AHDH), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, depression (including adolescent depression and minor depression), dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder (GAD), inhalation disorders, intoxication disorders (alcohol addiction), obesity (*i.e.*, reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic
 25 disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luctal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizotypal disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), social phobia (including social anxiety disorder),
 30 specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a patient who fails to maintain a

103

100

satisfactory response to SSRI therapy after an initial satisfactory response).
Reference to treatments for "nicotine addiction" herein also includes treatments
for smoking cessation. Many of the foregoing human conditions are generally
described by the American Psychiatric Association in their publication entitled,
"Diagnostic and Statistical Manual of Mental Disorders," 4th ed. rev.
(Washington D.C. 1994), the disclosure of which is hereby incorporated by
reference. General descriptions of addictive disorders, including disorders
related to intoxication and inhalants and, and nicotine addiction may be found
in many standard references, such as R.E. Hales *et al.*, "The American
Psychiatric Press Textbook of Psychiatry," 3d. ed. (1999), the disclosure of
which is hereby incorporated by reference.

The administration of (S,S) reboxetine is very effective in the
treatment of addictive disorders and withdrawal syndromes, adjustment
disorders, apathy, attention-deficit hyperactivity disorder, attention-deficit
disorders due to medical conditions, bulimia nervosa, chronic fatigue,
depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine
addiction, panic disorder, post-traumatic stress disorder, premenstrual
dysphoric disorder, schizoaffective disorder, and SSRI "poop out" syndrome.
Furthermore, the administration of (S,S) reboxetine is especially effective in
treatment of the addictive disorders and withdrawal syndromes, apathy,
attention-deficit hyperactivity disorder, attention-deficit disorders due to
medical conditions, chronic fatigue, dysthymic disorder, depression, nicotine
addiction, obesity, post-traumatic stress disorder, and SSRI "poop out"
syndrome.

It is known that commercially-available reboxetine is a racemic
mixture of the (R,R) and (S,S) enantiomers of 2-[(2-
ethoxyphenoxy)(phenyl)methyl]morpholine. It has now been discovered that
the (S,S) stereoisomer is the most active and the most selective stereoisomer
with respect to inhibiting the reuptake of norepinephrine. In addition, when
administered to an individual, in the dosages described herein, as an optically

104
101

pure material (*i.e.*, in the substantial absence of its (R,R) diastereomer), the individual does not experience many of the adverse side effects associated with the administration of commercially-available reboxetine. Furthermore, it has further been discovered that the (S,S) and (R,R) enantiomers have a reversed selectivity for the norepinephrine neurotransmitter in relation to the serotonin neurotransmitter, and an optically pure (S,S) reboxetine is significantly more effective at inhibiting reuptake of norepinephrine than either the (R,R) enantiomer or a racemic mixture of the (S,S) and (R,R) enantiomers.

Specifically, it has been found that compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Accordingly, the typical daily dosage of the racemic mixture (*i.e.*, commercially available reboxetine) can be reduced by about 50% to about 80% when using an optically pure (S,S) reboxetine. The reduction in dosage does not lead to a reduction in efficacy, but the reduction or elimination of various adverse side effects was observed.

In particular, because an optically pure (S,S) reboxetine selectively inhibits norepinephrine reuptake compared to serotonin reuptake, adverse side effects associated with serotonin reuptake are reduced or eliminated. Such adverse side effects include, but are not limited to, gastrointestinal disturbances, anxiety, sexual dysfunction, and undesirable side effects associated with drug-drug interactions.

The synthesis of a racemic mixture of reboxetine is disclosed in Melloni *et al.* U.S. Patent No. 4,229,449. Individual stereoisomers of reboxetine can be obtained by resolution of the racemic mixture of enantiomers using conventional methods generally known by those skilled in the art. Such methods include, but are not limited to, resolution by simple crystallization and chromatographic techniques, for example, as set forth in GB 2,167,407.

105
102

5 The compounds of this invention may be administered in oral
unit dosage forms such as tablets, capsules, pills, powders, or granules. They
may also be introduced parenterally, (e.g., subcutaneously, intravenously, or
intramuscularly), using forms known in the pharmaceutical art. They also may
10 be administered rectally or vaginally in such forms as suppositories or bougies.
These compounds also may be administered transdermally, such as with a
“patch” containing active ingredient. In general, the preferred route of
administration is oral, with a once or twice a day administration. The dosage
regimen and amount for treating patients with the compounds of this invention
15 is selected in accordance with a variety of factors including, for example, the
type, age, weight, sex, and medical condition of the patient, the severity of the
condition, the route of administration and the particular compound employed,
either racemate or pure enantiomer. An ordinarily skilled physician or
psychiatrist can readily determine and prescribe an effective amount of the
20 compound to prevent or arrest the progress of the condition. In so proceeding,
the physician or psychiatrist could employ relatively low dosages at first,
subsequently increasing the dose until a maximum response is obtained. In
general, reboxetine has a good safety profile and requires minimal titration.

25 Pharmaceutical compositions suitable for oral reboxetine
administration can be of any convenient form, such as sachets, tablets, capsules,
pills, or aerosol sprays, each containing a predetermined amount of the active
compound either as a powder or granules, or as a solution or a suspension in an
aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-
oil liquid emulsion. Such compositions can be prepared by any method that
30 includes the step of bringing the active compound either into intimate
association with a carrier, which constitutes one or more necessary or desirable
ingredients. Generally, the compositions are prepared by uniformly and
intimately admixing the active ingredient with liquid carriers or finely divided
solid carriers or both, and then, if necessary, shaping the product into a desired
form.

For example, a tablet can be prepared by compression or molding techniques, optionally, using one or more accessory ingredients. Compressed tablets can be prepared by compressing the active ingredient in a suitable machine into a free-flowing form, such as a powder or granules.

5 Thereafter, the compressed, free-flowing form optionally can be mixed with a binders, diluents, lubricants, disintegrating agents, effervescing agents, dyestuffs, sweeteners, wetting agents, and non-toxic and pharmacologically inactive substances typically present in pharmaceutical compositions. Molded

10 tablets can be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine.

Suitable binders for use in the pharmaceutical preparation include, for example, starches, gelatine, methylcellulose, gum arabic, tragacanth, and polyvinylpyrrolidone. Suitable diluents for use in the pharmaceutical preparation include, for example, lactose, dextrose, sucrose,

15 mannitol, sorbitol, and cellulose. Suitable lubricants for use in the pharmaceutical preparation include, for example, silica, talc, stearic acid, magnesium or calcium stearate, and or polyethylene glycols. Suitable disintegrating agents for use in the pharmaceutical preparation include, for example, starches, alginic acid, and alginates. Suitable wetting agents for use

20 in the pharmaceutical preparation include, for example, lecithin, polysorbates, and laurylsulfates. Generally, any effervescing agents, dyestuffs, and/or sweeteners known by those of ordinary skill in the art can be used in the preparation of a pharmaceutical composition.

Desirably, daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 10 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably,

25 each does of the composite contains about 0.5 to about 8 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. Even more preferably, however, each dose contains from about

30 0.5 to about 5 mg of the active ingredient, optically-pure (S,S) reboxetine, and

107
104

is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 2.5 mg to be administered in one or two oral doses. This will allow for tablets containing 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5 mg of optically pure (S,S) reboxetine.

In another embodiment, a preferred daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 0.9 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably, each dose of the composition contains about 0.5 to about 0.8 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. Even more preferably, however, each dose contains from about 0.5 to about 0.75 mg of the active ingredient, optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 0.9 mg to be administered in one oral dose.

Patients suffering from depression, nicotine addiction, conduct disorder, oppositional defiant disorder, and/or attention-deficit hyperactivity disorder will benefit from the administration of optically pure (S,S) reboxetine regardless of these or other co-morbid conditions. Diagnostic criteria for these disorders generally are provided by the American Psychiatric Association and published in their "Diagnostic and Statistical Manual of Mental Disorders," 4th ed. rev. (Washington D.C. 1994), and in International Publication Nos. WO 99/15177, WO 99/15176, and WO 99/15163, the disclosures of which are hereby incorporated by reference.

Furthermore, patients suffering from addictive disorders and withdrawal syndromes, adjustment disorders, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, bulimia nervosa, chronic fatigue, depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine addiction, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, schizoaffective disorder, and

108
105

SSRI "poop out" syndrome will benefit from the administration of optically pure (S,S) reboxetine.

5 These disorders display similar patterns in children, adolescents, and adults. Hence, methods of the present invention are effective in the treatment of child, adolescent, and adult patients. For purposes of the present invention, a child is considered to be a person below the age of puberty, an adolescent is considered to be a person between the age of puberty and up to about 18 years of age, and an adult generally is a person of at least about 18 years of age. As previously noted, the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient.

As stated above, reboxetine acts as an antidepressant. Reboxetine, however, does not act like most antidepressants. Unlike tricyclic antidepressants, and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that reboxetine is not a selective serotonin reuptake inhibitor. Rather, reboxetine is selective for the noradrenergic system. Reboxetine is not an SSRI, but is a novel, selective, noradrenaline reuptake inhibitor (NRI). B. Leonard, "Noradrenaline in basic models of depression." *European-Neuropsychopharmacol*, 7 Suppl. 1 pp. S11-6 and S71-3 (Apr., 1997). Unlike most prior generation drugs, reboxetine is a highly selective norepinephrine reuptake inhibitor, with only marginal serotonin and no dopamine reuptake inhibitory activity. Reboxetine displays no anticholinergic binding activity in different animal models, and is devoid of monoamine oxidase (MAO) inhibitory activity.

Reboxetine also is highly potent, pharmacologically specific, and fast acting agent. Investigations indicate that reboxetine has potent antireserpine activity, and combines the inhibitory properties of classical tricyclic antidepressants on the reuptake of noradrenaline with an ability to

desensitize β -adrenergic receptor function, without showing any appreciable blocking action at muscarinic, cholinergic, histaminergic, and α -adrenergic receptors. Moreover, reboxetine shows less vagolytic activity than tricyclic antidepressants, and no evidence of cardiotoxicity.

5 Accordingly, in another embodiment of the invention, racemic reboxetine can be used to treat a number of mental and neurological disorders. Specifically, reboxetine has been found particularly useful for treating or enhancing the treatment of a variety of psychiatric symptoms or disorders, with greater efficacy and with fewer side effects than with treatment by known
10 drugs. Furthermore, reboxetine may also be used to treat, or to enhance the treatment of, other specific psychiatric symptoms or disorders.

667020-8967703
15 Mental and neurological disorders that may be treated by administration of a therapeutically effective amount of a racemic reboxetine (or a derivative or pharmaceutically acceptable salts thereof) include, but are not limited to adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood); age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, bipolar disorder,
20 bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), obesity (*i.e.*, reducing the weight of obese or overweight patients), peripheral
25 neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luctal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizopreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), specific developmental disorders, and selective
30 serotonin reuptake inhibition (SSRI) "poop out" syndrome.

110
107

5 The racemate form of reboxetine is well tolerated and has a wide safety range. Racemic reboxetine can be administered to an individual in an amount in a range of about 2 to about 20 milligrams per patient per day (mg/day), and preferably about 4 to about 10 mg/day, and more preferably about 6 to about 10 mg/day. Depending upon the formulation and the individual's disorder, the total daily dosage can be administered in small amounts up to two times a day. Reboxetine typically is administered orally, for example, in the form of tablets, but can be administered parentally, transdermally, rectally, or vaginally.

10 A preferred method of administering racemic reboxetine is oral dosing once or twice a day. It can also be administered at dosages of about 2, 4, 6, 8, 10, or 12 mg/day or fractions thereof. For example, suitable administrations could be about 4 mg in the morning and about 2 or about 4 mg in the afternoon or evening. In some patients, the ideal dosing would be about 15 3 to about 5 mg in the morning and about 3 to about 5 mg in the afternoon. A skilled physician or psychiatrist can determine the precise level of dosing. The ideal dosing is routinely determined by an evaluation of clinical trials and the needs of specific patients.

20 In accordance with the present invention, the racemic reboxetine also can be administered as the free base or a pharmaceutically acceptable salt thereof. The phrases "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases as described above with respect to the salts of optically pure 25 (S,S) reboxetine. A preferred pharmaceutical salt of reboxetine is methanesulfonate (*i.e.*, mesylate), which is prepared using methanesulfonic acid.

30 Treatment of above disorders involves the administration of reboxetine in a manner and form that result in a reduction in the symptoms of the disease or disorder. Typically, the symptoms exhibited by children,

adolescents, and adults are similar to each other. Hence, methods of the present invention are effective in the treatment of child, adolescent, and adult patients.

5

EXAMPLE

This example demonstrates the superior selectivity of (S,S) reboxetine compared to its (R,R) stereoisomer and to racemic reboxetine.

10

Sprague-Dawley rats weighing about 250 to about 300 grams were decapitated, and cerebral cortical tissue was removed immediately.

15

Cerebral cortices were homogenized in nine volumes of medium each containing 0.32 M sucrose using a rotating pestle. The obtained homogenate was centrifuged at about 1000 x g for about 10 minutes at about 4°C. A supernatant was collected and further centrifuged at about 20,000 x g for about 20 minutes at a temperature of about 4°C. A protein pellet resulting from the centrifuge steps was re-suspended in a Kreb's-Hepes buffer to result in a protein concentration of about 2 mg/ml of buffer. The buffer was maintained at a pH of about 7.0 and contained: 20 mM Hepes; 4.16 mM NaHCO₃; 0.44 mM KH₂PO₄; 0.63 mM NaH₂PO₄; 127 mM NaCl; 5.36 mM KCl; 1.26 mM CaCl₂; and 0.98 mM MgCl₂.

20

25

Protein/buffer suspension was introduced into 166 assay tubes such that about 30 µg (10⁻⁶ grams) to about 150 µg of the protein was added to each of 166 assay tubes (i.e., 80 assays per transporter assay). Synaptosomal uptake of ³H-norpinephrine was determined as follows. About 1.4 nanomolar of [³H]citalopram and about 1.9 nM of [³H]nisoxetine were used to label serotonin and norepinephrine reuptake sites, respectively. Nonspecific binding was defined by 100 micromolar (µM) fluoxetine (for serotonin) and 10 µM desipramine (for norepinephrine). Incubation in total assay volume of about 500 microliters (µl) was carried out for about 60 minutes (for serotonin) and 120 minutes (for norepinephrine). Both incubations were carried out at about

109
+2

25°C, and terminated by rapid filtration through a 48-well cell harvester though GFB filters (pre-soaked with about 0.5 PEI for about 4 hours) in a 3 x 5 ml of ice-cold 200 mM tris-HCl, pH 7.0. Punched-out filters were placed into 7 ml minivials and radioactive assayed by liquid scintillation counting.

5 The ability of reboxetine (*i.e.*, racemic mixture of (R,R) and (S,S) reboxetine), (R,R) reboxetine, and (S,S) reboxetine to bind to norepinephrine and serotonin reuptake sites was evaluated in binding assays using the two radioligands, [³H]citalopram and [³H]nisoxetine. The concentration of the test compound required to inhibit 50% of the ³H-norpinephrine accumulation and ³H-serotonin (IC₅₀ values) were determined by linear regression analysis. A conversion of IC₅₀ values to Ki values was carried out using the Cheng-Prassoff equation presented below:

$$K_i = IC_{50} / (1 + ([L] / [K_d \text{ of } L]))$$

15 wherein [L] is the radioligand concentration used in nM, and K_d is the binding affinity of L in nM.

 The Ki values calculated according to the Cheng-Prassoff equation are provided in the table below:

Table			
Compound	Norepinephrine Reuptake (Ki nM)	Serotonin Reuptake (Ki nM)	Selectivity of Ki of Serotonin/Norepinephrine
(S,S) Reboxetine	0.23 ± 0.06	2937 ± 246	12,770
(R,R) Reboxetine	7.0 ± 1.7	104 ± 43	15
Reboxetine	1.6 ± 0.6	129 ± 13	81

20 The data shows that (S,S) reboxetine is about five to about eight fold more potent than the reboxetine racemate with respect to inhibiting the reuptake of norepinephrine. In addition, racemic reboxetine has an 81 fold selectivity favoring norepinephrine reuptake inhibition over serontonin reuptake inhibition. Unexpectedly, the enantiomeric selectivity of the (S,S) and (R,R)

110-113
reboxetine stereoisomers with respect to inhibiting the reuptake of norepinephrine and serotonin are quite different. The (S,S) enantiomer is very poor with respect to inhibiting reuptake of serotonin (*i.e.*, a high K_i) and, therefore, has a surprisingly high selectivity for the norepinephrine reuptake site. In particular, the selectivity of serotonin versus norepinephrine increases from 81 (for the racemate) to 12,770 for an optically pure (S,S) reboxetine. Accordingly, administration of a therapeutic dose of (S,S) reboxetine effectively inhibits norepinephrine reuptake, but serotonin reuptake essentially is not affected. As a consequence, adverse side effects associated with the inhibition of serotonin reuptake are not manifested.

Surprisingly, this effect is not observed with (R,R) reboxetine, but are quite to the contrary. (R,R) reboxetine is a weaker inhibitor than (S,S) reboxetine with respect to norepinephrine reuptake, *i.e.*, affinity (*i.e.*, K_i) for (R,R) reboxetine is 7 nM whereas the K_i for (S,S) reboxetine is 0.23 nM. In addition, (R,R) reboxetine is much more effective at inhibiting serotonin uptake than (S,S) reboxetine, *i.e.*, K_i for (R,R) reboxetine is 104 nM, whereas the K_i for (S,S) reboxetine is 2937 nM. Accordingly, (R,R) reboxetine has a low selectivity for norepinephrine reuptake inhibition versus serotonin reuptake inhibition.

The surprisingly high potency of the (S,S) enantiomer over both the racemate and (R,R) reboxetine provides a treating physician an ability to prescribe an effective dosage of a norepinephrine reuptake inhibitor, *i.e.*, (S,S) reboxetine, that is about 10% to about 20% of the current daily dosage of reboxetine (racemate) to achieve the same reuptake inhibition at the norepinephrine site. In addition, the surprisingly high inhibition selectivity of an optically pure (S,S) reboxetine essentially limits inhibition to norepinephrine reuptake, thereby reducing adverse side effects associated with inhibiting the reuptake of serotonin.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood

11-24

therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

65T020-896T4T09

112 43

What is claimed is:

1. A method of treating a human suffering from a condition wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

2. The method of claim 1 wherein said (S,S) reboxetine is administered in an amount of about 0.1 to about 10 mg/day.

3. The method of claim 2 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 8 mg/day.

4. The method of claim 3 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 5 mg/day.

5. The method of claim 4 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 2.5 mg/day.

6. The method of claim 5 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.9 mg/day.

7. The method of claim 6 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.8 mg/day.

8. The method of claim 7 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.75 mg/day.

001020-895 F.H.O.S

9. The method of claim 1 wherein said (S,S) reboxetine is administered orally, parenterally, transdermally, rectally, or vaginally.

10. The method of claim 9 wherein said (S,S) reboxetine is orally administered with a pharmaceutically acceptable carrier comprising at least one of a binder, diluent, lubricant, disintegrating agent, effervescing agent, dyestuff, sweetener, and wetting agent.

11. The method of claim 10 wherein the oral administration is by a sachet, capsule, tablet, or aerosol spray.

12. The method of claim 9 wherein said (S,S) reboxetine is parenterally administered subcutaneously, intravenously, or intramuscularly.

13. The method of claim 1, wherein the pharmaceutically acceptable salt is methanesulfonate.

14. The method of claim 1 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 90 wt.% of (S,S) reboxetine, and less than about 10 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

15. The method of claim 14 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 97 wt.% of (S,S) reboxetine and less than about 3 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

16. The method of claim 15 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 99 wt.% of (S,S) reboxetine and less than about 1 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

001020-896T4.09

17. The method of claim 1 wherein said condition is at least one of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

18. The method of claim 17 wherein the addictive disorder comprises an addiction to at least one of alcohol, nicotine, and other psychoactive substances.

19. The method of claim 17 wherein the adjustment disorder comprises depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood.

20. The method of claim 17 wherein the age-associated learning and mental disorder comprises Alzheimer's disease.

21. The method of claim 17 wherein the depression comprises adolescent depression and minor depression.

22. The method of claim 17 wherein the premenstrual dysphoric disorder comprises premenstrual syndrome and late luctal phase dysphoric disorder.

115
170

23. The method of claim 17 wherein the psychotic disorder comprises schizophrenia, schizoaffective and schizopreniform disorders.

24. The method of claim 17 wherein social phobia comprises social anxiety disorder.

25. The method of claim 17 wherein the sleep disorder comprises narcolepsy and enuresis.

26. The method of claim 17 wherein somatoform disorders comprise somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS.

27. The method of claim 17 wherein said condition is at least one of an adjustment disorder, an age-associated learning or mental disorder, apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, bulimia nervosa, chronic fatigue, cyclothymic disorder, depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine addiction, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, and SSRI "poop out" syndrome.

28. The method of claim 27 wherein said condition is at least one of apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, chronic fatigue, cyclothymic disorder, depression, nicotine addiction, post-traumatic stress disorder, and SSRI "poop out" syndrome.

6014968-070129

116
119

29. A method of treating a human suffering from a condition wherein inhibiting reuptake of norepinephrine provides a benefit, while diminishing adverse side effects, the method comprising the steps of administering a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

30. The method of claim 29 wherein said adverse affects comprise dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in males, anticholinergic-like effects, and side effects with drug-drug interactions.

31. A method of treating a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine or a pharmaceutically acceptable salt thereof to an individual, wherein said disorder is at least one of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorders, a specific developmental disorders, and SSRI "poop out" syndrome.

32. The method of claim 31 wherein said disorder is at least one of an adjustment disorder, an age-associated learning or mental disorder, apathy, bulimia nervosa, chronic fatigue, cyclothymic disorder, dysthymic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, and SSRI "poop out" syndrome.

561020-090709

117 120
118

33. The method of claim 32 wherein said disorder is at least one of apathy, chronic fatigue, cyclothymic disorder, post-traumatic stress disorder, and SSRI "poop out" syndrome

34. The method of claim 31 wherein the reboxetine is administered to the individual in an amount of about 2 to about 20 mg/day.

35. The method of claim 34 wherein the reboxetine is administered to the individual in an amount of about 4 to about 10 mg/day.

36. The method of claim 35 wherein the reboxetine is administered to the individual in an amount of about 6 to about 10 mg/day.

37. The method of claim 31 wherein said reboxetine is administered orally, parenterally, transdermally, rectally, or vaginally.

38. The method of claim 37 wherein said reboxetine is orally administered with a pharmaceutically acceptable carrier comprising at least one of a binder, diluent, lubricant, disintegrating agent, effervescing agent, dyestuff, sweetener, and wetting agent.

39. The method of claim 38 wherein the oral administration is by a sachet, capsule, tablet, or aerosol spray.

40. The method of claim 37 wherein said reboxetine is parenterally administered subcutaneously, intraveously, or intramuscularly.

41. The method of claim 31 wherein the pharmaceutically acceptable salt is methanesulfonate.

42. A preparation of a medicament from a composition comprising reboxetine to treat at least one nervous system disorder selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

43. Use of reboxetine in a manufacture of a medicament to treat at least one nervous system disorder selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

557020-336F4ES

Junio 28, 2000
Traducción Oficial No.0282
REF:PHARMACIA & UPJOHN CO.
Patente No.60/144,131

(Pharmacia & Upjohn)
Caso-28341/62484

120 24

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
OFICINA DE MARCAS Y PATENTES

Junio 06, 2000

Por medio del presente documento se certifica que adjunta se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud: 60/144,131

Fecha de Registro: Julio 16, 1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma: P. SWAIN

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes realizado de color dorado.

Edwards Calado

121 25

HOJA DE SOLICITUD PROVISIONAL
EN LA OFICINA DE MARCAS Y PATENTES DE LOS
ESTADOS UNIDOS

Expediente No. : 28341/6248.1

TRAMITE PARA SOLICITUD PROVISIONAL DE PATENTE

Correo:
Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Estimados Señores:

Por medio de la presente solicitamos una Patente Provisional bajo el Código 37 de
Regulaciones Federales § 1.53 (c) de los siguientes inventores:

1. Erik H. F. Wong
7352 Hampstead Lane
Portage, Michigan 49024
2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49002
3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071

Edmundo Calado N.

122 126

4. Robert MacArthur
531 Carrington Court
Kalamazoo, Michigan 49009

5. Duncan P. Taylor
8722 West F. Avenue
Kalamazoo, Michigan 49009

**Título: METODOS ORIGINALES PARA INHIBIR LA REASIMILACION
DE LA NOREPINEFRINA**

1. PARTES DE LA SOLICITUD INCLUIDAS

- 1 Título
- 25 Páginas de especificaciones (no incluyendo Reivindicaciones y resumen)
- 7 Páginas de reivindicaciones
- 1 Página resumen

CERTIFICADO DE CORREO POSTAL (37 CFR 1.10)

Yo, por medio del presente documento certifico que, el trámite provisional de patente y los documentos que hacen referencia a la misma, han sido enviados por Correo Certificado de Los Estados Unidos en la fecha de Julio 16, 1999, en un sobre rotulado al Comisionado Asistente para Patentes, Box Provisional Patent Application, Washington, DC., 20231. mediante el Servicio de Correo Certificado al Destinatario del Servicio Postal de los Estados Unidos, bajo el envío número EM099538478US.

Firma: Richard Zimmermann

Eduardo Calasso

123 + 27
1

Documentos adicionales Adjuntos

- ☐ Certificado de Deposito Biológico
- ☐ Un disco que contiene nucleotidos y/o secuencia de amino
ácidos en formato legible por computadora.
- ☐ Programa de Computadora Microficha
- ☐ Declaraciones verificadas de reivindicaciones de estatus de Pequeña empresa
bajo el Código de Regulaciones Federales 1.9 y 1.27
- ☐ Poder
- ☐ Traducción Oficial de solicitudes de patente en otro idioma aparte del inglés.
- ☐ Transferencia del Invento
- ☒ Sobre con timbre prepago
- ☐ Otros Honorarios (ej. copia juramentada)

3. Cálculo de Registro Honorarios (37 CFR 1.16)

- ☒ Solicitud provisional (\$75.00/\$150.00 Honorarios registro : \$150.00
 - ☐ Otros Honorarios (ej. Registro de Traspaso) Honorarios registro: _____
- Total de Honorarios adjuntos \$150.00

4. Forma de Pago de Honorarios

- ☒ Se adjunta cheque de la Empresa por la suma de: \$150.00
 - ☐ Cobrar a Cuenta Corriente No. 13.2855 por la suma de: _____
- Se anexa una copia de este Trámite

- ☐ No se anexa copia de trámite

5. Por medio de la presente el Comisionado está autorizado para cobrar deficiencias en el monto adjunto o cualquier honorario adicional que se requiera durante la vigencia de

Eduardo Calado
Comisionado
3

1
124 178

esta solicitud bajo el Código de Regulaciones Federales 37 §1.16 o Código de Regulaciones Federales 37 §1.17 o bajo cualquier otra regulación aplicable (a excepción del pago de los Honorarios por emisión) a la Cuenta Corriente No. 13.2855. Se adjunta una copia de este trámite.

Favor reembolsar cualquier sobrepago a: Marshall, O'Toole, Gersnstein, Murray & Borum a la dirección a continuación:

Favor dirigir todas las llamadas a : James Napoli a la siguiente dirección:

Atentamente,

MARSHALL, OTOOLE, GERNSTEIN, MURRAY & BORUM

6300 Sears Tower

233 South Wacker Drive

Chicago, Illinois 60606-6402

Tel: (312) 474-6300

Eduardo Calandran
Eduardo Calandran
Eduardo Calandran
Eduardo Calandran
Eduardo Calandran

125 129

COINVENTORES

Expediente No. 28341/6248.1

CERTIFICADO DE CORREO POSTAL

Servicio Postal, CORREO INMEDIATO, bajo el envío número EM099538478US.

Yo por el presente certifico que este documento (u honorarios), han sido enviados por Correo Certificado de Los Estados Unidos "CORREO POSTAL INMEDIATO AL DESTINATARIO" bajo el código 37 Código de Regulaciones Federales §1.10 en la fecha indicada anteriormente y rotulado a: Box Provisional Patent Application, Assistant Commissioner for patents, Washington, D.C.

Richard Zimmermann

SOLICITUD PROVISIONAL PARA CARTAS DE PATENTES
DE LOS ESTADOS UNIDOS

ESPECIFICACION

A todos aquellos a quien pueda interesar:

Informamos que nosotros , Erik H. F. Wong, ciudadano de los Estados Unidos de América, residente en 7352 Hampstead lane, portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, ciudadano de los Estados Unidos de América, residente en 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall,

Edward Calvo
11-8

un ciudadano del Reino Unidos, residente en 7560 Fieldwood Circle, Mattawan, Michigan, 49071, Van Buren County; Robert MacArthur, ciudadano del Reino Unido y Canadá, residente En 531 Carrington Court, Kalamazoo, Michigan, 49009, Kalamazoo County; y Duncan P. Taylor, ciudadano de los Estados Unidos de America, residente en 8722 West F. Avenue, Kalamazoo, Michigan, 49009, Kalamazoo County, son autores del invento original e útil, llamado "METODOS ORIGINALES PARA INHIBIR LA REASIMILACION DE LA NOREPINEFRINA", sobre la cual la siguiente es una especificación:

Abogados solicitantes:

James J. Napoli (No Reg. 32, 361

Marshall, O'Toole, Gerstein, Murray & Borum

6300 Sears Tower

233 South Wacker Drive

Chicago, Illinois 60606-6402

Eduardo Celado R.

REIVINDICACIONES:

1. Un método para tratar el sufrimiento humano de una condición, en el cual los inhibidores de norepinefrina proporcionan un beneficio. El método consiste en el suministro de una cantidad terapéuticamente eficaz de una reboxetina ópticamente pura (S,S), o una sal farmacéuticamente aceptable de la misma, a dicha reboxetina individual ópticamente pura (S, S) siendo esta substancialmente libre de reboxetina (R, R).

2. Un método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.1 hasta alrededor de 10 mg/día.

3. El método de acuerdo a la reivindicación 2 en el cual dicha reboxetina (S, S) se suministra aproximadamente 0.5 hasta alrededor de 8 mg/día.

4. El método de acuerdo a la Reivindicación 3 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 5mg/día.

Eduardo Calado

5. El método de acuerdo a la Reivindicación 4 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 2.5 mg/día.

6. El método de acuerdo a la Reivindicación 5 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.9 mg/día.

7. El método de acuerdo a la Reivindicación 6 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.8 mg/día.

8. El método de acuerdo a la Reivindicación 7 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.75 mg/día.

9. El método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra por vía oral, parenteral, transdermico, rectal o vaginal.

Eduardo Palacios

10. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra oralmente con un portador farmacéuticamente aceptable el cual consta de por lo menos una substancia aglutinante, diluyente, lubricante, agente desintegrante, agente efervescente, materia colorante, dulcificante y agente húmedo.

11. El método de acuerdo a la reivindicación 10 en el cual el suministro oral es mediante un sachet, cápsula, tableta o aerosol.

12. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra parenteralmente subcutánea, intravenosa o intramuscular.

13. El método de acuerdo a la Reivindicación 1, en la cual la sal farmacéuticamente aceptable es metanosulfonado.

14. El método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) o sal farmacéuticamente aceptable del mismo, consiste de aproximadamente 90% de peso de la reboxetina (S,S) o inferior de alrededor 10% del peso de la reboxetina (S, S) basado en el peso total de la reboxetina presente.

Eduardo Calado

15. El método de acuerdo a la Reivindicación 14 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, consiste de aproximadamente por lo menos 97% del peso de reboxetina (S, S) e inferior de alrededor de 3 % del peso de la Reboxetina (S, S), basado en el peso total de la reboxetina presente.

16. El método de acuerdo a la Reivindicación 15 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, consiste de aproximadamente por lo menos 99% del peso de reboxetina (S, S) e inferior de alrededor de 1 % del peso de la Reboxetina (S, S), basado en el peso total de la reboxetina presente.

17. El método de acuerdo a la reivindicación 1 en el cual dicha condición es de por lo menos un trastorno adictivo y síndrome de abstinencia, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica,

Calvardo Calvardo

trastorno de conducta, trastorno ciclotimia, depresión, trastorno distímico, fibromialgia y otros trastornos somáticos, trastorno de ansiedad generalizada, trastornos de inhalación, trastornos de intoxicación, obesidad, trastorno obsesivo -compulsivo y trastornos relacionados con el espectro, trastorno de desafío de oposición, trastorno de pánico, neuropatía periférica, trastorno de estres post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno afectivo temporal, trastorno del sueño, fobia social, trastorno de desarrollo específico y inhibidores de serotonina selectiva (SSRI), síndrome de defecarse.

18. El método de acuerdo a la reivindicación 17 en la cual los trastornos adictivos consisten de una adicción de por lo menos un alcohol, nicotina y otras sustancias psicoactivas.

19. El método de acuerdo a la reivindicación 17 en la cual los trastornos de acoplamiento constan de estado de ánimo depresivo, ansiedad, ansiedad mezclada y ánimo depresivo, alteración en la conducta y alteraciones en la conducta combinadas con el estado de ánimo.

Eduardo Calado

- 136
132
20. El método de acuerdo a la reivindicación 17 en la cual los trastornos de aprendizaje relacionados con la edad y trastornos mentales consiste del mal de Alzheimer's.
21. El método de acuerdo a la reivindicación 17 en la cual la depresión consiste de depresión adolescente o depresión menor.
22. El método de acuerdo a la reivindicación 17 en la cual el trastorno disfórico premenstrual consiste del síndrome premenstrual y trastorno disfórico en fase tardía luteal.
23. El método de acuerdo a la reivindicación 17 en la cual el trastorno sicótico cosiste de esquizofrenia, esquizoactivo y trastorno sicoafectivo.
24. El método de acuerdo a la reivindicación 17 en la cual la fobia social consiste de trastorno de ansiedad social.
25. El método de acuerdo a la reivindicación 17 en la cual el trastorno del sueño consiste de narcolepsia y enuresis.

Edward Calabro

26. El método de acuerdo a la reivindicación 17 en la cual el trastorno somático consiste de trastornos de somatización, trastorno de conversión, trastorno de dolor, hipocondría, trastorno de dismorfia corpórea, trastorno no identificado somático y somatoformas NOS.

27. El método de acuerdo a la reivindicación 17 en el cual dicha condición es de por lo menos un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, depresión, trastorno distímico, trastorno de ansiedad generalizada (GAD), adicción a la nicotina, trastorno de estrés post-traumático, trastorno disfórico premenstrual, trastorno sicótico, y (SSRI), síndrome de defecarse.

28. El método de acuerdo a la reivindicación 27 en el cual dicha condición es por lo menos una de apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, síndrome de fatiga crónica, trastorno

Calvardo Calado

ciclotímico, depresión, adicción a la nicotina, trastorno de stress post-traumático, y (SSRI), síndrome de defecarse.

29. Un método para tratar un sufrimiento debido a una condición en el cual los inhibidores de norepinefrina proporcionan un beneficio, mientras que disminuye los efectos secundarios, el método consiste en suministrar una dosis total aproximada de 0.1 hasta alrededor de 10mg/día de una reboxetina. (S, S) ópticamente pura o una sal farmacéuticamente aceptable del mismo, a un individuo, siendo dicha reboxetina (S, S) ópticamente pura y substancialmente libre de (R,R) reboxetina.

30. El método de acuerdo a la reivindicación 29 en la cual dichos efectos adversos consisten de mareos, insomnio, atolondrado, cambios en presión sanguínea, sudores, trastornos intestinales, disfunción sexual en hombres, efectos parecidos a anticolinérgicos, y efectos secundarios con interacción de drogas-drogas.

31. Un método para el tratamiento de trastornos del sistema nervioso, el cual consiste en los siguientes pasos: el suministro de una dosis terapéuticamente eficaz de reboxetina racémica o una sal farmacéuticamente aceptable del mismo a un individuo que necesite

Charles Calabrese

dicho tratamiento, en el cual dicho trastorno es por lo menos uno de los trastornos de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno de desarrollo específico, y (SSRI), síndrome de defecarse.

32. El método de acuerdo a la reivindicación 31 en el cual el trastorno es de por lo menos uno de los trastornos de acoplamiento, trastorno de déficit de aprendizaje debido a la edad, o trastorno mental, apatía, bulimia nervosa, fatiga crónica, trastorno ciclotímico, trastorno distímico, trastorno de estres post traumático, trastorno disfórico premenstrual, trastorno sicótico, y (SSRI) síndrome de defecarse .

33. El método de acuerdo a la reivindicación 32, en el cual dicho trastorno es por lo menos unos relacionado con la apatía, fatiga

Edwards Calades

crónica, trastorno ciclotímico, trastorno de estrés post traumático y
SSRI síndrome de defecarse.

140
136

34. El método de acuerdo a la reivindicación 31, en el cual la reboxetina se suministra al individuo en una cantidad aproximada de 2 hasta 20 mg/día.

35. El método de acuerdo a la reivindicación 34, en el cual la reboxetina se suministra en una cantidad aproximadamente de 4 hasta 10 mg/día.

36. El método de acuerdo a la reivindicación 35, en la cual la reboxetina se suministra aproximadamente de 6 hasta 10 mg/día.

37. El método de acuerdo a la reivindicación 31, en el cual dicha reboxetina se suministra por vía oral, parenteral, transdérmica, rectal o vaginal.

38. El método de acuerdo a la reivindicación 37, en la cual dicha reboxetina se suministra oralmente con un portador farmacéuticamente aceptable, el cual consta de por lo menos un menos una sustancia aglutinante, diluyente, lubricante, agente

Edwards Calado

desintegrante, agente efervescente, materia colorante, dulcificante y agente húmedo.

39. El método de acuerdo a la reivindicación 38 en el cual el suministro oral es mediante un sachet, cápsula, tableta o aerosol.

40. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra parenteralmente subcutánea, intravenosa o intramuscular.

41. El método de acuerdo a la Reivindicación 1, en la cual la sal farmacéuticamente aceptable es metanosulfonado.

42. Una preparación de un medicamento de una composición que consta de reboxetina para tratar por lo menos un trastorno del sistema nervioso seleccionado del grupo que consiste de trastorno de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad y trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de

Edwards Calles

142
138
stress post-traumático, trastorno disfórico premenstrual, trastorno
sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno
de desarrollo específico, y (SSRI), síndrome de defecarse.

43. El uso de la reboxetina para la fabricación de un medicamento
para tratar por lo menos un trastorno del sistema nervioso
seleccionado de un grupo que consiste de trastornos de acoplamiento,
un trastorno de acoplamiento, trastorno de aprendizaje asociado con
la edad y trastorno mental, anorexia nervosa, apatía, trastorno por
déficit de atención debido a condiciones médicas generales, trastorno
bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno
ciclotímico, trastorno distímico, fibromialgia y otros trastornos
somáticos, obesidad, neuropatía periférica, trastorno de stress post-
traumático, trastorno disfórico premenstrual, trastorno sicótico,
trastorno temporal afectivo, trastorno de insomnio, trastorno de
desarrollo específico, y (SSRI), síndrome de defecarse

Eduardo Calado

PA 258500

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 06, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/144,131

FILING DATE: July 16, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

A/PROV 144

140

07/16/99
Jc408 U.S. PTO

Jc508 U.S. PTO
60/144131
07/16/99

PROVISIONAL PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No: 28341/6248.1

PROVISIONAL PATENT APPLICATION TRANSMITTAL

Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the provisional patent application under 37 CFR 1.53(c) of

Inventors:

- | | |
|---|---|
| 1. Erik H.F. Wong,
7352 Hampstead Lane
Portage, Michigan 49024 | 4. Robert McArthur
531 Carrington Court
Kalamazoo, Michigan 49009 |
| 2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49002 | 5. Duncan P. Taylor
8722 West F Avenue
Kalamazoo, Michigan 49009 |
| 3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071 | |

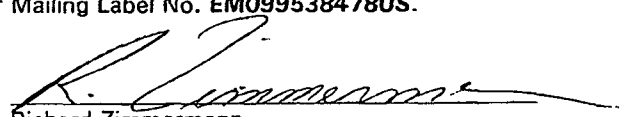
Title: NEW TREATMENTS FOR SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

1. Application Papers Enclosed

- | | |
|----|--|
| 1 | Title Page |
| 25 | Pages of Specification (excluding Claims & Abstract) |
| 7 | Pages of Claims |
| 1 | Page of Abstract |

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Provisional Patent Application Transmittal and the documents referred to as enclosed therewith are being deposited with the United States Postal Service on July 16, 1999, in an envelope addressed to the Assistant Commissioner for Patents, Box Provisional Patent Application, Washington, D.C. 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing Label No. EM099538478US.


Richard Zimmermann

60144131-071699

145

141

2. Additional Papers Enclosed

- ☐ Declaration of Biological Deposit
- ☐ Computer readable copy of sequence listing containing nucleotide and/or amino acid sequence
- ☐ Microfiche computer program
- ☐ Verified statement(s) claiming small entity status under 37 CFR 1.9 and 1.27
- ☐ Associate power of attorney
- ☐ Verified translation of a non-English patent application
- ☐ An assignment of the invention
- ☒ Return Receipt Postcard
- ☐ Other (e.g. declaration or oath)

3. Filing Fee Calculation (37 CFR 1.16)

- ☒ Provisional Application (\$75.00/\$150.00) Filing Fee: \$150.00
- ☐ Other Fees (e.g. Recording Assignment) Filing Fee: \$_____

Total Fees Enclosed \$150.00

4. Method of Payment of Fees

- ☒ Enclosed is our firm check in the amount of: \$150.00
- ☐ Charge Deposit Account No. 13-2855 in the amount of: \$_____
- ☐ Not enclosed

A copy of this Transmittal is enclosed.

5. Deposit Account and Refund Authorization

The Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees which may be required during the pendency of this application under 37 CFR 1.16 or 37 CFR 1.17 or under other applicable rules (except payment of issue fees), to Deposit Account No. 13-2855. A copy of this Transmittal is enclosed.

Please refund any overpayment to Marshall, O'Toole, Gerstein, Murray & Borun at the address below.

604431.0700

146

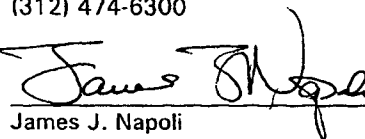
142

Please direct all future communications to James J. Napoli, at the address below.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

By:



James J. Napoli
Reg. No: 32,361

July 16, 1999

669720" TERTHOS

JOINT INVENTORS

Attorney Docket No. 28341/6248.1

143

"EXPRESS MAIL" mailing label No. EM099538478US.

Date of Deposit: July 16, 1999

I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231



Richard Zimmermann

PROVISIONAL APPLICATION FOR
UNITED STATES LETTERS PATENT

S P E C I F I C A T I O N

TO ALL WHOM IT MAY CONCERN:

Be it known that we, Erik H.F. Wong, a citizen of the United States of America, residing at 7352 Hampstead Lane, Portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, a citizen of the United States of America, residing at 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall, a citizen of the United Kingdom, residing at 7560 Fieldwood Circle, Mattawan, Michigan, 49071, Van Buren County; Robert McArthur, a citizen of the United Kingdom and Canada, residing at 531 Carrington Court, Kalamazoo, Michigan, 49009, Kalamazoo County; and Duncan P. Taylor, a citizen of the United States of America, residing at 8722 West F Avenue, Kalamazoo, Michigan, 49009, Kalamazoo County, have invented new and useful "NEW TREATMENTS FOR SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS," of which the following is a specification.

Attorneys for Applicants:

James J. Napoli (Reg. No. 32,361)
Marshall, O'Toole, Gerstein,
Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402

669720-TEF44709

1/4/00

144

NEW TREATMENTS FOR SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods of treating individuals suffering from a variety of conditions wherein inhibiting reuptake of norepinephrine provides a benefit. In particular, the present invention relates to methods of treatment comprising administration of reboxetine to an individual to selectively inhibit the reuptake of norepinephrine.

Brief Description of Related Technology

Many types of depression, mental, behavioral, and neurological disorders originate from disturbances in brain circuits that convey signals using certain monoamine neurotransmitters. Monoamine neurotransmitters include, for example, norepinephrine (noradrenaline), serotonin (5-HT), and dopamine. Lower-than-normal levels of norepinephrine are associated with a variety of symptoms including lack of energy, motivation, and interest in life. Thus, a normal level of norepinephrine is essential to maintaining drive and capacity for reward.

These neurotransmitters travel from the terminal of a neuron across a small gap (*i.e.*, the synaptic cleft) and bind to receptor molecules on

the surface of a second neuron. This binding elicits intracellular changes that initiate or activate a response or change in the postsynaptic neuron.

Inactivation occurs primarily by transport (*i.e.*, reuptake) of the neurotransmitter back into the presynaptic neuron. Abnormality in noradrenergic transmission results in various types of depression, mental, behavioral, and neurological disorders attributed to a variety of symptoms including a lack of energy, motivation, and interest in life. *See generally*, R.J. Baldessarini, "Drugs and the Treatment of Psychiatric Disorders: Depression and Mania" in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, NY, NY, pp. 432-439 (1996).

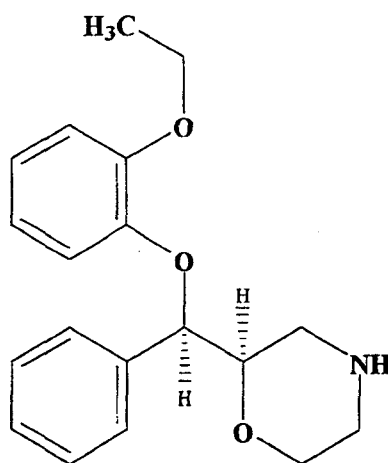
Reboxetine (*i.e.*, 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine) raises the concentration of physiologically active norepinephrine by preventing reuptake of norepinephrine, for example. Reboxetine is a norepinephrine reuptake inhibitor and has been shown to be effective in the short-term (*i.e.*, less than eight weeks) and long-term treatment of depression. In fact, reboxetine has been shown to have effectiveness that is similar to fluoxetine, imipramine, and desipramine, commonly prescribed antidepressants, in both adults and elderly patients. *See* S.A. Montgomery, *Reboxetine: Additional Benefits to the Depressed Patient*, *Psychopharmacol (Oxf)* 11:4 Suppl., S9-15 (Abstract) (1997).

Antidepressant drugs are sometimes divided into "generations." The first generation included the monoamine oxidase inhibitors (such as isocarboxazid and phenylhydrazine) and tricyclic agents (such as imipramine). The second generation of antidepressant drugs included compounds such as mianserin and trazodone. The third generation has included drugs called selective reuptake inhibitors (*e.g.*, fluoxetine, sertraline, paroxetine, and reboxetine). Those drugs were characterized by relatively selective action on only one of the three main monoamine systems thought to be involved in depression (*i.e.*, 5-HT (serotonin), noradrenaline (norepinephrine), and dopamine). APP Textbook of Psychopharmacology (A.F. Schatzberg and C.B.

Nemeroff), American Psychiatric Press, 2d. ed., (1998); Lexicon of Psychiatry, Nuerology and the Neurosciences (F.J. Ayd, Jr.) Williams and Wilkins (1995). The antidepressant efficacy of reboxetine is evidenced by its ability to prevent reserpine-induced blepharospasm and hypothermia in mice, down regulation of β -adrenergic receptors and desensitization of noradrenaline-coupled adenylate cyclase. See M. Brunello and G. Racagni, "Rationale for the Development of Noradrenaline Reuptake Inhibitors," Human Psychopharmacology, vol. 13, S-13-519, Supp. 13-519 (1998).

Reboxetine generally is described in Melloni *et al.* U.S. Patent Nos. 4,229,449, 5,068,433, and 5,391,735, and in GB 2,167,407, the disclosures of which are hereby incorporated by reference. Chemically, reboxetine has two chiral centers and, therefore, exists as two enantiomeric pairs of diastereomers, shown below as isomers (I) through (IV):

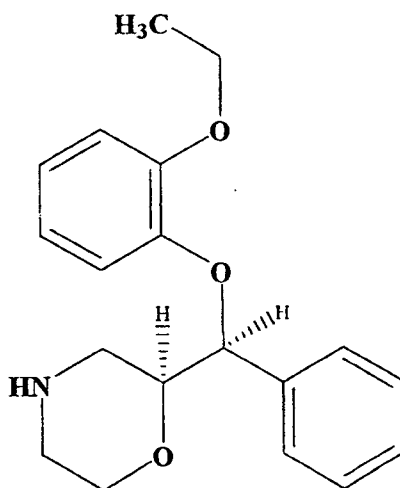
(I)



(R, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

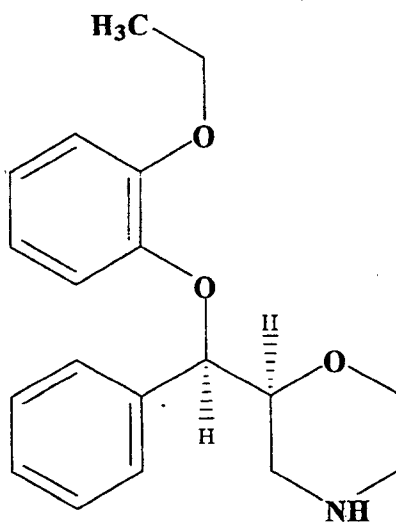
15
147

(II)



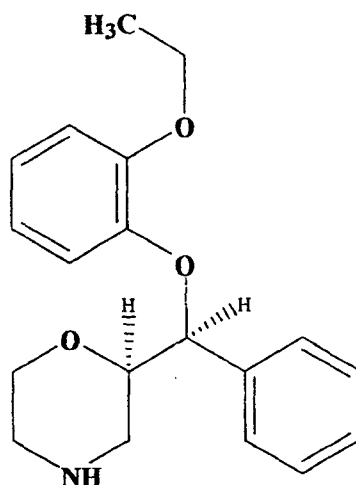
(S, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

(III)



(R, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

(IV)



(S, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes D and L, or (+) or (-), designate the sign of rotation of plane-polarized light by the compound, with L or (-) meaning that the compound is levorotatory. In contrast, a compound prefixed with D or (+) is dextrorotatory. There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. Thus, D-lactic acid is the same as (-)-lactic acid, and L-lactic acid is the same as (+)-lactic acid. For a given chemical structure, each of a pair of enantiomers are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric, or racemic, mixture.

Stereochemical purity is important in the pharmaceutical field, where many of the most often prescribed drugs exhibit chirality. For example, the L-enantiomer of the beta-adrenergic blocking agent, propranolol, is known

to be 100 times more potent than its D-enantiomer. Additionally, optical purity is important in the pharmaceutical drug field because certain isomers have been found to impart a deleterious effect, rather than an advantageous or inert effect. For example, it is believed that the D-enantiomer of thalidomide is a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, whereas its corresponding L-enantiomer is believed to be a potent teratogen.

When two chiral centers exist in one molecule, there are four possible stereoisomers: (R,R), (S,S), (R,S), and (S,R). Of these, (R,R) and (S,S) are an example of a pair of enantiomers (mirror images of each other), which typically share chemical properties and melting points just like any other enantiomeric pair. The mirror images of (R,R) and (S,S) are not, however, superimposable on (R,S) and (S,R). This relationship is called diastereoisomeric, and the (S,S) molecule is a diastereoisomer of the (R,S) molecule, whereas the (R,R) molecule is a diastereoisomer of the (S,R) molecule.

Currently, reboxetine is commercially available only as a racemic mixture of enantiomers, (R,R) and (S,S) in a 1:1 ratio, and reference herein to the generic name "reboxetine" refers to this enantiomeric, or racemic, mixture. Reboxetine is commercially sold under the trade names of EDRONAX™, PROLIFT™, VESTRA™, and NOREBOX™. As previously noted, reboxetine has been shown to be useful in the treatment of human depression. Orally administered reboxetine is readily absorbed and requires once or twice a day administration. A preferred adult daily dose is in the range of about 8 to about 10 milligrams (mg). The effective daily dosage of reboxetine for a child is smaller, typically in a range of about 4 to about 5 mg. The optimum daily dosage for each patient, however, must be determined by a treating physician taking into account the patient's size, other medications which the patient may be taking, identity and severity of the particular disorder, and all of the other circumstances of the patient.

15A
150

Administration of reboxetine, however, can result in undesired side effects associated with drug-drug interactions and in other undesirable effects such as, for example, dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in males, certain anticholinergic-like effects (e.g., tachyarrhythmia and urinary retention).

Accordingly, there is a need in the art for a method of treating individuals suffering from a variety of conditions where inhibiting reuptake of norepinephrine provides a benefit, while reducing or eliminating the adverse side effects associated with conventional norepinephrine reuptake inhibitors. There also is a need for a method that selectively inhibits the reuptake of norepinephrine over other neurotransmitters, like serotonin and dopamine.

SUMMARY OF THE INVENTION

The present invention generally is directed to methods of treating or preventing a variety of conditions where inhibition of norepinephrine reuptake provides a benefit. More particularly, the present invention is directed to an effective treatment or prevention of such conditions comprising administration of reboxetine, or an optically pure (S,S) stereoisomer thereof, to a human. Individuals treated with optically pure (S,S) reboxetine do not experience certain adverse side effects associated with the administration of the racemic mixture of (R,R) and (S,S) reboxetine. The present invention therefore includes administering optically pure (S,S) reboxetine to a human to selectively inhibit norepinephrine reuptake, and thereby control, reduce, or eliminate adverse effects caused by the administration of the racemic mixture of reboxetine.

More specifically, one embodiment of the present invention is directed to a method of treating or preventing a human condition wherein inhibiting reuptake of norepinephrine provides a benefit. The method

comprises the step of administering a therapeutic amount, typically about 0.5 to about 10 mg/day, of optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. Optically pure (S,S) reboxetine is substantially free of (R,R) reboxetine.

5 Human conditions that can be treated and/or prevented by
inhibiting the reuptake of norepinephrine include, but are not limited to,
addictive disorders (including those due to alcohol, nicotine, and other
psychoactive substances) and withdrawal syndrome, adjustment disorders
10 (including depressed mood, anxiety, mixed anxiety and depressed mood,
disturbance of conduct, and mixed disturbance of conduct and mood), age-
associated learning and mental disorders (including Alzheimer's disease),
anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to
general medical conditions, attention-deficit hyperactivity disorder (ADHD),
bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder,
15 cyclothymic disorder, depression (including adolescent depression and minor
depression), dysthymic disorder, fibromyalgia and other somatoform disorders
(including somatization disorder, conversion disorder, pain disorder,
hypochondriasis, body dysmorphic disorder, undifferentiated somatoform
disorder, and somatoform NOS), generalized anxiety disorder (GAD),
20 inhalation disorders, intoxication disorders (alcohol addiction), migraine
headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients),
obsessive compulsive disorders and related spectrum disorders, oppositional
defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress
disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late
25 luteal phase dysphoric disorder), psychotic disorders (including schizophrenia,
schizoaffective and schizophreniform disorders), seasonal affective disorder,
sleep disorders (such as narcolepsy and enuresis), social phobia (including
social anxiety disorder), specific developmental disorders, and selective
serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a
30 patient who fails to maintain a satisfactory response to SSRI therapy after an
initial period of satisfactory response).

Optically pure (S,S) reboxetine is advantageous over prior treatment or prevention methods which utilized a racemic mixture of (R,R) and (S,S) reboxetine. In particular, it has been found that treatments using compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Therefore, reuptake blockage can be achieved with much lower dosages. Accordingly, the present invention may permit a substantial reduction in the customary daily dosage of the racemic mixture (*i.e.*, the commercially available reboxetine) by about 50% to about 80% because of the use of an optically pure (S,S) reboxetine. In addition, treatments utilizing the optically pure (S,S) reboxetine may result in fewer undesirable adverse side effects associated with the treatment because of the high selectivity and potency of (S,S) reboxetine with respect to inhibiting the reuptake of norepinephrine.

Another embodiment of the present invention is directed to a method of treating or preventing a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine to an individual, wherein the disorder is at least one of adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), migraine headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients), peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizophreniform

6044433.071699

disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome. Other embodiments of the present invention are directed to a preparation of a medicament from a composition comprising reboxetine and a use of reboxetine in a manufacture of the medicament to treat or prevent at least one of the aforementioned nervous system disorders.

Additional benefits and features of the present invention will become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the example and the appended claims. It should be noted, however, that while the invention is susceptible of embodiments in various forms, described hereafter are specific preferred embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reboxetine is a known compound that is active on the central nervous system. Reboxetine has been used as an antidepressant, and has been suggested for the treatment of oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder. These proposed treatments are disclosed in International Publication Nos. WO 99/15163, WO 95/15176, and WO 99/15177.

Heretofore, use of reboxetine has been limited to the treatment of depression, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder. Furthermore, prior treatment methods using reboxetine administered a racemic mixture of the (S,S) and (R,R) stereoisomers. One embodiment of the present invention, however, is directed to an effective method using an optically pure (S,S) stereoisomer of reboxetine

to treat or prevent conditions wherein inhibition of reuptake of norepinephrine is beneficial. (S,S) Reboxetine is an effective, selective inhibitor of norepinephrine reuptake and, accordingly, dose levels can be substantially reduced in comparison to racemic reboxetine. In addition, individuals treated with an optically pure (S,S) reboxetine do not experience certain adverse effects associated with the administration of the racemic mixture of (R,R) and (S,S) reboxetine. Accordingly, one embodiment of the present invention includes administering a therapeutic amount of an optically pure (S,S) reboxetine to a human to inhibit the reuptake of norepinephrine, and to control, reduce, or eliminate adverse effects associated with administration of racemic reboxetine.

More specifically, one embodiment of the present invention is directed to a method of treating or preventing a human condition wherein inhibiting reuptake of norepinephrine provides a benefit. The method comprises the step of administering, and preferably orally administering, a total dose of about 0.5 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual. The optically pure (S,S) reboxetine is substantially free of (R,R) reboxetine.

As used herein, the term "reboxetine" refers to the racemic mixture of the (R,R) and (S,S) enantiomers of reboxetine. In contrast, the term "(S,S) reboxetine" refers to only the (S,S) stereoisomer. Similarly, the term "(R,R) reboxetine" refers to only the (R,R) stereoisomer.

The phrases "optically pure (S,S) reboxetine" and "substantially free of its (R,R) stereoisomer," as used herein, mean that the composition contains a greater proportion of (S,S) reboxetine in relation to (R,R) reboxetine. In a preferred embodiment, the phrases mean that the composition is at least 90 percent by weight (wt.%) of (S,S) reboxetine, and 10 wt.% or less of (R,R) reboxetine. In a more preferred embodiment the phrases mean that the composition contains at least 97 wt.% of (S,S) reboxetine, and 3 wt.% or less of (R,R) reboxetine. In an even more preferred embodiment, the phrases

mean that the composition contains at least 99 wt.% of (S,S) reboxetine, and 1 wt.% or less of (R,R) reboxetine. In a most preferred embodiment, the phrases "optically pure (S,S) reboxetine" and "substantially free of its (R,R) stereoisomer," as used herein, mean that the composition contains greater than 5 99 wt.% of (S,S) reboxetine. The foregoing percentages are based upon the total amount of reboxetine present in the composition. The phrases "substantially free of (R,R) reboxetine," "substantially optically pure (S,S) stereoisomer of reboxetine," "substantially optically pure (S,S) reboxetine," "optically pure (S,S) stereoisomer of reboxetine," and "optically pure (S,S) 10 reboxetine" are also encompassed by the above-described amounts.

669120-TEST-109
The phrases "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases. Because the active compound (*i.e.*, (S,S) reboxetine) used in 15 the present invention is basic, salts may be prepared from pharmaceutically acceptable acids. Suitable pharmaceutically acceptable acids include acetic, benzenesulfonic (besylate), benzoic, p-bromophenylsulfonic, camphorsulfonic, carbonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, isethionic, lactic, maleic, malic, mandelic, 20 methanesulfonic (mesylate), mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. Examples of such pharmaceutically acceptable salts of (S,S) reboxetine, thus, include, but are not limited to, acetate, benzoate, β -hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, 25 citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, 30 phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite,

156

sulfonate, tartrate, xylenesulfonate, and the like. A preferred pharmaceutical salt of (S,S) reboxetine is methanesulfonate (*i.e.*, mesylate), which is prepared using methanesulfonic acid.

5 The phrases "adverse effects" and "adverse side effects" in relation to reboxetine include, but are not limited to, dizziness, insomnia, lightheadedness, changes in blood pressure, gastrointestinal disturbances, sexual dysfunction in males, extrapyramidal side effects, certain anticholinergic-like effects (*e.g.*, tachycardia, blurred vision), and undesired side effects associated with with drug-drug interactions.

10 More specifically, administration of an optically pure (S,S) reboxetine is effective in treating and/or preventing various human conditions including, but not limited to, addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances) and withdrawal syndrome, adjustment disorders (including depressed mood, anxiety, mixed
15 anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic
20 fatigue syndrome, conduct disorder, cyclothymic disorder, depression (including adolescent depression and minor depression), dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized
25 anxiety disorder (GAD), inhalation disorders, intoxication disorders (alcohol addiction), migraine headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*,
30 premenstrual syndrome and late luteal phase dysphoric disorder), psychotic

00441.0469

161

152

00444-0409

disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial satisfactory response). Reference to treatments for "nicotine addiction" herein also includes treatments for smoking cessation. Many of the foregoing human conditions are generally described by the American Psychiatric Association in their publication entitled, "Diagnostic and Statistical Manual of Mental Disorders," 4th ed. rev. (Washington D.C. 1994), the disclosure of which is hereby incorporated by reference. General descriptions of addictive disorders, including disorders related to intoxication and inhalants and, and nicotine addiction may be found in many standard references, such as R.E. Hales *et al.*, "The American Psychiatric Press Textbook of Psychiatry," 3d. ed. (1999), the disclosure of which is hereby incorporated by reference.

As noted above, (S,S) reboxetine also can be used to prevent or treat migraine headaches. Furthermore, (S,S) reboxetine can be used to treat or prevent headaches in migraineurs or people suffering from migraine headaches, including the treatment of symptoms of an existing headache, treatment to prevent the occurrence, intensity, and duration of a headache, prophylactic use to prevent or reduce the incidence or duration of migraines, as an adjuvant to facilitate the effectiveness of an abortive medication or co-administered with other medications (including abortive medications) to reduce the required dosages (and side effects) of those medications.

As used herein, the terms "treat," "treatment," and "treating," extend to prophylaxis, in other words "prevent," "prevention," and "preventing," as well as treatment of established conditions. Accordingly, use of the terms "prevent," "prevention," and "preventing," would be an administration of the pharmaceutical composition to a person who has in the

158

past suffered from the aforementioned conditions, such as, for example, migraine headaches, but is not suffering from the conditions at the moment of the composition's administration.

5 The administration of (S,S) reboxetine is very effective in the treatment and/or prevention of addictive disorders and withdrawal syndromes, adjustment disorders, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, bulimia nervosa, chronic fatigue, depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine addiction, panic disorder, post-traumatic stress disorder, premenstrual
10 dysphoric disorder, schizoaffective disorder, and SSRI "poop out" syndrome. Furthermore, the administration of (S,S) reboxetine is especially effective in treatment or prevention of addictive disorders and withdrawal syndromes, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, chronic fatigue, dysthymic disorder, depression, nicotine
15 addiction, obesity, post-traumatic stress disorder, and SSRI "poop out" syndrome.

It is known that commercially-available reboxetine is a racemic mixture of the (R,R) and (S,S) enantiomers of 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine. It has now been discovered that
20 the (S,S) stereoisomer is the most active and the most selective stereoisomer with respect to inhibiting the reuptake of norepinephrine. In addition, when administered to an individual, in the dosages described herein, as an optically pure material (*i.e.*, in the substantial absence of its (R,R) diastereomer), the individual does not experience many of the adverse side effects associated with
25 the administration of commercially-available reboxetine. Furthermore, it has further been discovered that the (S,S) and (R,R) enantiomers have a reversed selectivity for the norepinephrine neurotransmitter in relation to the serotonin neurotransmitter, and an optically pure (S,S) reboxetine is significantly more effective at inhibiting reuptake of norepinephrine than either the (R,R)
30 enantiomer or a racemic mixture of the (S,S) and (R,R) enantiomers.

665129 TESTES

163

Specifically, it has been found that compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Accordingly, the typical daily dosage of the racemic mixture (*i.e.*, commercially available reboxetine) can be reduced by about 50% to about 80% when using an optically pure (S,S) reboxetine. The reduction in dosage does not lead to a reduction in efficacy, but the reduction or elimination of various adverse side effects was observed.

In particular, because an optically pure (S,S) reboxetine selectively inhibits norepinephrine reuptake compared to serotonin reuptake, adverse side effects associated with serotonin reuptake are reduced or eliminated. Such adverse side effects include, but are not limited to, gastrointestinal disturbances, anxiety, sexual dysfunction, and undesirable side effects associated with drug-drug interactions.

The synthesis of a racemic mixture of reboxetine is disclosed in Melloni *et al.* U.S. Patent No. 4,229,449. Individual stereoisomers of reboxetine can be obtained by resolution of the racemic mixture of enantiomers using conventional methods generally known by those skilled in the art. Such methods include, but are not limited to, resolution by simple crystallization and chromatographic techniques, for example, as set forth in GB 2,167,407.

The compounds of this invention may be administered in oral unit dosage forms such as tablets, capsules, pills, powders, or granules. They may also be introduced parenterally, (*e.g.*, subcutaneously, intravenously, or intramuscularly), using forms known in the pharmaceutical art. They also may be administered rectally or vaginally in such forms as suppositories or bougies. These compounds also may be administered transdermally, such as with a "patch" containing active ingredient. In general, the preferred route of administration is oral, with a once or twice a day administration. The dosage regimen and amount for treating patients with the compounds of this invention is selected in accordance with a variety of factors including, for example, the

type, age, weight, sex, and medical condition of the patient, the severity of the condition, the route of administration and the particular compound employed, either racemate or pure enantiomer. An ordinarily skilled physician or psychiatrist can readily determine and prescribe an effective amount of the compound to prevent or arrest the progress of the condition. In so proceeding, the physician or psychiatrist could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained. In general, reboxetine has a good safety profile and requires minimal titration.

Pharmaceutical compositions suitable for oral reboxetine administration can be of any convenient form, such as sachets, tablets, capsules, pills, or aerosol sprays, each containing a predetermined amount of the active compound either as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions can be prepared by any method that includes the step of bringing the active compound either into intimate association with a carrier, which constitutes one or more necessary or desirable ingredients. Generally, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into a desired form.

For example, a tablet can be prepared by compression or molding techniques, optionally, using one or more accessory ingredients. Compressed tablets can be prepared by compressing the active ingredient in a suitable machine into a free-flowing form, such as a powder or granules. Thereafter, the compressed, free-flowing form optionally can be mixed with a binders, diluents, lubricants, disintegrating agents, effervescing agents, dyestuffs, sweeteners, wetting agents, and non-toxic and pharmacologically inactive substances typically present in pharmaceutical compositions. Molded tablets can be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine.

161

Suitable binders for use in the pharmaceutical preparation include, for example, starches, gelatine, methylcellulose, gum arabic, tragacanth, and polyvinylpyrrolidone. Suitable diluents for use in the pharmaceutical preparation include, for example, lactose, dextrose, sucrose, mannitol, sorbitol, and cellulose. Suitable lubricants for use in the pharmaceutical preparation include, for example, silica, talc, stearic acid, magnesium or calcium stearate, and or polyethylene glycols. Suitable disintegrating agents for use in the pharmaceutical preparation include, for example, starches, alginic acid, and alginates. Suitable wetting agents for use in the pharmaceutical preparation include, for example, lecithin, polysorbates, and laurylsulfates. Generally, any effervescing agents, dyestuffs, and/or sweeteners known by those of ordinary skill in the art can be used in the preparation of a pharmaceutical composition.

Desirably, daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 10 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably, each dose of the composite contains about 0.5 to about 8 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. Even more preferably, however, each dose contains from about 0.5 to about 5 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 2.5 mg to be administered in one or two oral doses. This will allow for tablets containing 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5 mg of optically pure (S,S) reboxetine.

In another embodiment, a preferred daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 0.9 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably, each dose of the composition contains about 0.5 to about 0.8 mg of the active ingredient, optically-pure (S,S) reboxetine,

and is substantially free of its (R,R) stereoisomer. Even more preferably, however, each dose contains from about 0.5 to about 0.75 mg of the active ingredient, optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 0.9 mg to be administered in one oral dose.

Patients suffering from depression, nicotine addiction, conduct disorder, oppositional defiant disorder, and/or attention-deficit hyperactivity disorder will benefit from the administration of optically pure (S,S) reboxetine regardless of these or other co-morbid conditions. Diagnostic criteria for these disorders generally are provided by the American Psychiatric Association and published in their "Diagnostic and Statistical Manual of Mental Disorders," 4th ed. rev. (Washington D.C. 1994), and in International Publication Nos. WO 99/15177, WO 99/15176, and WO 99/15163, the disclosures of which are hereby incorporated by reference.

Furthermore, patients suffering from addictive disorders and withdrawal syndromes, adjustment disorders, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, bulimia nervosa, chronic fatigue, depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine addiction, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, schizoaffective disorder, and SSRI "poop out" syndrome will benefit from the administration of optically pure (S,S) reboxetine.

These disorders display similar patterns in children, adolescents, and adults. Hence, methods of the present invention are effective in the treatment of child, adolescent, and adult patients. For purposes of the present invention, a child is considered to be a person below the age of puberty, an adolescent is considered to be a person between the age of puberty and up to about 18 years of age, and an adult generally is a person of at least about 18 years of age. As previously noted, the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's

163

size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient.

As stated above, reboxetine acts as an antidepressant.

Reboxetine, however, does not act like most antidepressants. Unlike tricyclic antidepressants, and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that reboxetine is not a selective serotonin reuptake inhibitor. Rather, reboxetine is selective for the noradrenergic system. Reboxetine is not an SSRI, but is a novel, selective, noradrenaline reuptake inhibitor (NRI). B. Leonard, "Noradrenaline in basic models of depression." *European-Neuropsychopharmacol*, 7 Suppl. 1 pp. S11-6 and S71-3 (Apr., 1997). Unlike most prior generation drugs, reboxetine is a highly selective norepinephrine reuptake inhibitor, with only marginal serotonin and no dopamine reuptake inhibitory activity. Reboxetine displays no anticholinergic binding activity in different animal models, and is devoid of monoamine oxidase (MAO) inhibitory activity.

Reboxetine also is a highly potent, pharmacologically specific, and fast acting agent. Investigations indicate that reboxetine has potent antireserpine activity, and combines the inhibitory properties of classical tricyclic antidepressants on the reuptake of noradrenaline with an ability to desensitize β -adrenergic receptor function, without showing any appreciable blocking action at muscarinic, cholinergic, histaminergic, and α -adrenergic receptors. Moreover, reboxetine shows less vagolytic activity than tricyclic antidepressants, and no evidence of cardiotoxicity.

Accordingly, in another embodiment of the invention, racemic reboxetine can be used to treat or prevent a number of mental and neurological disorders. Specifically, reboxetine has been found particularly useful for treating or enhancing the treatment or prevention of a variety of psychiatric symptoms or disorders, with greater efficacy and with fewer side effects than with treatment by known drugs. Furthermore, reboxetine may also be used to

treat, or to enhance the treatment or prevention of, other specific psychiatric symptoms or disorders.

Mental and neurological disorders that may be treated or prevented by administration of a therapeutically effective amount of a racemic reboxetine (or a derivative or pharmaceutically acceptable salts thereof) include, but are not limited to adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), migraine headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients), peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

Similar to (S,S) reboxetine, racemic reboxetine also can be used to treat humans suffering from migraine headaches, particularly to reduce the frequency, duration, intensity, and or complications resulting from migraine headaches. Furthermore, racemic reboxetine can be used to prevent migraine headaches.

The racemate form of reboxetine is well tolerated and has a wide safety range. Racemic reboxetine can be administered to an individual in an amount in a range of about 2 to about 20 milligrams per patient per day

(mg/day), and preferably about 4 to about 10 mg/day, and more preferably about 6 to about 10 mg/day. Depending upon the formulation and the individual's disorder, the total daily dosage can be administered in small amounts up to two times a day. Reboxetine typically is administered orally, for example, in the form of tablets, but can be administered parentally, transdermally, rectally, or vaginally.

A preferred method of administering racemic reboxetine is oral dosing once or twice a day. It can also be administered at dosages of about 2, 4, 6, 8, 10, or 12 mg/day or fractions thereof. For example, suitable administrations could be about 4 mg in the morning and about 2 or about 4 mg in the afternoon or evening. In some patients, the ideal dosing would be about 3 to about 5 mg in the morning and about 3 to about 5 mg in the afternoon. A skilled physician or psychiatrist can determine the precise level of dosing. The ideal dosing is routinely determined by an evaluation of clinical trials and the needs of specific patients.

In accordance with the present invention, the racemic reboxetine also can be administered as the free base or a pharmaceutically acceptable salt thereof. The phrases "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases as described above with respect to the salts of optically pure (S,S) reboxetine. A preferred pharmaceutical salt of reboxetine is methanesulfonate (*i.e.*, mesylate), which is prepared using methanesulfonic acid.

Treatment or prevention of above disorders involves the administration of reboxetine in a manner and form that result in a reduction in the symptoms of the disease or disorder. Typically, the symptoms exhibited by children, adolescents, and adults are similar to each other. Hence, methods of the present invention are effective in the treatment of child, adolescent, and adult patients.

163 40

EXAMPLE

This example demonstrates the superior selectivity of (S,S) reboxetine compared to its (R,R) stereoisomer and to racemic reboxetine.

5 Sprague-Dawley rats weighing about 250 to about 300 grams were decapitated, and cerebral cortical tissue was removed immediately. Cerebral cortices were homogenized in nine volumes of medium each containing 0.32 M sucrose using a rotating pestle. The obtained homogenate was centrifuged at about 1000 x g for about 10 minutes at about 4°C. A
10 supernatant was collected and further centrifuged at about 20,000 x g for about 20 minutes at a temperature of about 4°C. A protein pellet resulting from the centrifuge steps was re-suspended in a Kreb's-Hepes buffer to result in a protein concentration of about 2 mg/ml of buffer. The buffer was maintained at a pH of about 7.0 and contained: 20 mM Hepes; 4.16 mM
15 NaHCO₃; 0.44 mM KH₂PO₄; 0.63 mM NaH₂PO₄; 127 mM NaCl; 5.36 mM KCl; 1.26 mM CaCl₂; and 0.98 mM MgCl₂.

Protein/buffer suspension was introduced into 166 assay tubes such that about 30 µg (10⁻⁶ grams) to about 150 µg of the protein was added to each of 166 assay tubes (*i.e.*, 80 assays per transporter assay). Synaptosomal
20 uptake of ³H-norpinephrine was determined as follows. About 1.4 nanomolar of [³H]citalopram and about 1.9 nM of [³H]nisoxetine were used to label serotonin and norepinephrine reuptake sites, respectively. Nonspecific binding was defined by 100 micromolar (µM) fluoxetine (for serotonin) and 10 µM
25 desipramine (for norepinephrine). Incubation in total assay volume of about 500 microliters (µl) was carried out for about 60 minutes (for serotonin) and 120 minutes (for norepinephrine). Both incubations were carried out at about 25°C, and terminated by rapid filtration through a 48-well cell harvester though
30 GFB filters (pre-soaked with about 0.5 PEI for about 4 hours) in a 3 x 5 ml of ice-cold 200 mM tris-HCl, pH 7.0. Punched-out filters were placed into 7 ml minivials and radioactive assayed by liquid scintillation counting.

The ability of reboxetine (*i.e.*, racemic mixture of (R,R) and (S,S) reboxetine), (R,R) reboxetine, and (S,S) reboxetine to bind to norepinephrine and serotonin reuptake sites was evaluated in binding assays using the two radioligands, [³H]citalopram and [³H]nisoxetine. The concentration of the test compound required to inhibit 50% of the ³H-norpinephrine accumulation and ³H-serotonin (IC₅₀ values) were determined by linear regression analysis. A conversion of IC₅₀ values to Ki values was carried out using the Cheng-Prassoff equation presented below:

$$K_i = IC_{50} / (1 + ([L]/[K_d \text{ of } L])),$$

wherein [L] is the radioligand concentration used in nM, and K_d is the binding affinity of L in nM.

The Ki values calculated according to the Cheng-Prassoff equation are provided in the table below:

Table

Compound	Norepinephrine Reuptake (Ki nM)	Serotonin Reuptake (Ki nM)	Selectivity of Ki of Serotonin/Norepinephrine
(S,S) Reboxetine	0.23 ± 0.06	2937 ± 246	12,770
(R,R) Reboxetine	7.0 ± 1.7	104 ± 43	15
Reboxetine	1.6 ± 0.6	129 ± 13	81

The data shows that (S,S) reboxetine is about five to about eight fold more potent than the reboxetine racemate with respect to inhibiting the reuptake of norepinephrine. In addition, racemic reboxetine has an 81 fold selectivity favoring norepinephrine reuptake inhibition over serotonin reuptake inhibition. Unexpectedly, the enantiomeric selectivity of the (S,S) and (R,R) reboxetine stereoisomers with respect to inhibiting the reuptake of norepinephrine and serotonin are quite different. The (S,S) enantiomer is very poor with respect to inhibiting reuptake of serotonin (*i.e.*, a high Ki) and, therefore, has a surprisingly high selectivity for the norepinephrine reuptake

site. In particular, the selectivity of serotonin versus norepinephrine increases from 81 (for the racemate) to 12,770 for an optically pure (S,S) reboxetine. Accordingly, administration of a therapeutic dose of (S,S) reboxetine effectively inhibits norepinephrine reuptake, but serotonin reuptake essentially is not affected. As a consequence, adverse side effects associated with the inhibition of serotonin reuptake are not manifested.

Surprisingly, this effect is not observed with (R,R) reboxetine, but are quite to the contrary. (R,R) reboxetine is a weaker inhibitor than (S,S) reboxetine with respect to norepinephrine reuptake, *i.e.*, affinity (*i.e.*, K_i) for (R,R) reboxetine is 7 nM whereas the K_i for (S,S) reboxetine is 0.23 nM. In addition, (R,R) reboxetine is much more effective at inhibiting serotonin uptake than (S,S) reboxetine, *i.e.*, K_i for (R,R) reboxetine is 104 nM, whereas the K_i for (S,S) reboxetine is 2937 nM. Accordingly, (R,R) reboxetine has a low selectivity for norepinephrine reuptake inhibition versus serotonin reuptake inhibition.

The surprisingly high potency of the (S,S) enantiomer over both the racemate and (R,R) reboxetine provides a treating physician an ability to prescribe an effective dosage of a norepinephrine reuptake inhibitor, *i.e.*, (S,S) reboxetine, that is about 10% to about 20% of the current daily dosage of reboxetine (racemate) to achieve the same reuptake inhibition at the norepinephrine site. In addition, the surprisingly high inhibition selectivity of an optically pure (S,S) reboxetine essentially limits inhibition to norepinephrine reuptake, thereby reducing adverse side effects associated with inhibiting the reuptake of serotonin.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

169 1790

What is claimed is:

1. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.
2. The method of claim 1 wherein said (S,S) reboxetine is administered in an amount of about 0.1 to about 10 mg/day.
3. The method of claim 2 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 8 mg/day.
4. The method of claim 3 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 5 mg/day.
5. The method of claim 4 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 2.5 mg/day.
6. The method of claim 5 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.9 mg/day.
7. The method of claim 6 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.8 mg/day.
8. The method of claim 7 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.75 mg/day.

00443.01699

170

9. The method of claim 1 wherein said (S,S) reboxetine is administered orally, parenterally, transdermally, rectally, or vaginally.

10. The method of claim 9 wherein said (S,S) reboxetine is orally administered with a pharmaceutically acceptable carrier comprising at least one of a binder, diluent, lubricant, disintegrating agent, effervescing agent, dyestuff, sweetener, and wetting agent.

11. The method of claim 10 wherein the oral administration is by a sachet, capsule, tablet, or aerosol spray.

12. The method of claim 9 wherein said (S,S) reboxetine is parenterally administered subcutaneously, intravenously, or intramuscularly.

13. The method of claim 1, wherein the pharmaceutically acceptable salt is methanesulfonate.

14. The method of claim 1 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 90 wt.% of (S,S) reboxetine, and less than about 10 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

15. The method of claim 14 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 97 wt.% of (S,S) reboxetine and less than about 3 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

16. The method of claim 15 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 99 wt.% of (S,S) reboxetine and less than about 1 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

669720-TEF4409

17H

17. The method of claim 1 wherein said condition is at least one of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

18. The method of claim 17 wherein the addictive disorder comprises an addiction to at least one of alcohol, nicotine, and other psychoactive substances.

19. The method of claim 17 wherein the adjustment disorder comprises depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood.

20. The method of claim 17 wherein the age-associated learning and mental disorder comprises Alzheimer's disease.

21. The method of claim 17 wherein the depression comprises adolescent depression and minor depression.

172

22. The method of claim 17 wherein the premenstrual dysphoric disorder comprises premenstrual syndrome and late luteal phase dysphoric disorder.

23. The method of claim 17 wherein the psychotic disorder comprises schizophrenia, schizoaffective and schizophreniform disorders.

24. The method of claim 17 wherein social phobia comprises social anxiety disorder.

25. The method of claim 17 wherein the sleep disorder comprises narcolepsy and enuresis.

26. The method of claim 17 wherein somatoform disorders comprise somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS.

27. The method of claim 17 wherein said condition is at least one of an adjustment disorder, an age-associated learning or mental disorder, apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, bulimia nervosa, chronic fatigue, cyclothymic disorder, depression, dysthymic disorder, generalized anxiety disorder, nicotine addiction, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, and SSRI "poop out" syndrome.

28. The method of claim 27 wherein said condition is at least one of apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, chronic fatigue, cyclothymic disorder, depression, nicotine addiction, post-traumatic stress disorder, and SSRI "poop out" syndrome.

29. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, while diminishing adverse side effects, the method comprising the steps of administering a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

30. The method of claim 29 wherein said adverse affects comprise dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in males, anticholinergic-like effects, and side effects with drug-drug interactions.

31. A method of treating or preventing a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine or a pharmaceutically acceptable salt thereof to an individual, wherein said disorder is at least one of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorders, a specific developmental disorders, and SSRI "poop out" syndrome.

32. The method of claim 31 wherein said disorder is at least one of an adjustment disorder, an age-associated learning or mental disorder, apathy, bulimia nervosa, chronic fatigue, cyclothymic disorder, dysthymic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, and SSRI "poop out" syndrome.

174

33. The method of claim 32 wherein said disorder is at least one of apathy, chronic fatigue, cyclothymic disorder, post-traumatic stress disorder, and SSRI "poop out" syndrome

34. The method of claim 31 wherein the reboxetine is administered to the individual in an amount of about 2 to about 20 mg/day.

35. The method of claim 34 wherein the reboxetine is administered to the individual in an amount of about 4 to about 10 mg/day.

36. The method of claim 35 wherein the reboxetine is administered to the individual in an amount of about 6 to about 10 mg/day.

37. The method of claim 31 wherein said reboxetine is administered orally, parenterally, transdermally, rectally, or vaginally.

38. The method of claim 37 wherein said reboxetine is orally administered with a pharmaceutically acceptable carrier comprising at least one of a binder, diluent, lubricant, disintegrating agent, effervescent agent, dyestuff, sweetener, and wetting agent.

39. The method of claim 38 wherein the oral administration is by a sachet, capsule, tablet, or aerosol spray.

40. The method of claim 37 wherein said reboxetine is parenterally administered subcutaneously, intravenously, or intramuscularly.

41. The method of claim 31 wherein the pharmaceutically acceptable salt is methanesulfonate.

42. A preparation of a medicament from a composition comprising reboxetine to treat or prevent at least one nervous system disorder selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

43. Use of reboxetine in a manufacture of a medicament to treat or prevent at least one nervous system disorder selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

126

ABSTRACT OF THE DISCLOSURE

Methods of treating humans suffering from, or preventing humans from suffering, depression, a mental, a behavioral, and/or a neurological condition where inhibiting reuptake of norepinephrine is a benefit are disclosed. The methods generally include administration of pharmaceutical compositions comprising reboxetine (2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine) or an optically pure (S,S) enantiomer thereof. Also disclosed are preparations of a medicament from a composition comprising reboxetine, and uses of reboxetine in a manufacture of the medicament to treat a human suffering from, or prevent a human from suffering, depression, a mental, a behavioral, and/or a neurological condition.

669T20-7574709

Junio 30, 2000
Traducción Oficial No.0284
REF:PHARMACIA & UPJOHN CO.
Patente No.60/158,256

(Pharmacia & Upjohn)
Caso-28341/62484

177

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
OFICINA DE MARCAS Y PATENTES

Junio 06, 2000

Por medio del presente documento se certifica que adjunta se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud: 60/158,256

Fecha de Registro: Octubre 06, 1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma: P. SWAIN

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes realizado de color dorado.

Edwards Caliendo

183
178

HOJA DE SOLICITUD PROVISIONAL
EN LA OFICINA DE MARCAS Y PATENTES DE LOS
ESTADOS UNIDOS

Expediente No. : 28341/6248.2

TRAMITE PARA SOLICITUD PROVISIONAL DE PATENTE

Correo:
Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Estimados Señores:

Por medio de la presente solicitamos una Patente Provisional bajo el Código 37 de
Regulaciones Federales § 1.53 (c) de los siguientes inventores:

1. Erik H. F. Wong
7352 Hampstead Lane
Portage, Michigan 49024
2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49002
3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071

Edwards Caladon

4. Robert MacArthur
531 Carrington Court
Kalamazoo, Michigan 49009

5. Duncan P. Taylor
8722 West F. Avenue
Kalamazoo, Michigan 49009

Título: INHIBIDORES ALTAMENTE SELECCIONADOS PARA LA
REASIMILACION DE LA NOREPINEFRINA Y METODOS UTILIZANDO LOS
MISMOS

1. PARTES DE LA SOLICITUD INCLUIDAS

- 1 Título
- 25 Páginas de especificaciones (no incluyendo Reivindicaciones y resumen)
- 7 Páginas de reivindicaciones
- 1 Página resumen

CERTIFICADO DE CORREO POSTAL (37 CFR 1.10)

Yo, por medio del presente documento certifico que, el trámite provisional de patente y los documentos que hacen referencia a la misma, han sido enviados por Correo Certificado de Los Estados Unidos en la fecha de Octubre 6, 1999, en un sobre rotulado al Comisionado Asistente para Patentes, Box Provisional Patent Application, Washington, DC., 20231, mediante el Servicio de Correo Certificado al Destinatario del Servicio Postal de los Estados Unidos, bajo el envío número EM099777946US.

Eduardo Calisto

Documentos adicionales Adjuntos

- ☐ Certificado de Deposito Biológico
- ☐ Un disco que contiene nucleotidos y/o secuencia de amino
ácidos en formato legible por computadora.
- ☐ Programa de Computadora Microficha
- ☐ Declaraciones verificadas de reivindicaciones de estatus de Pequeña empresa
bajo el Código de Regulaciones Federales 1.9 y 1.27
- ☐ Poder
- ☐ Traducción Oficial de solicitudes de patente en otro idioma aparte del inglés.
- ☐ Transferencia del Invento
- ☒ Sobre con timbre prepago
- ☐ Otros Honorarios (ej. copia juramentada)

3. Cálculo de Registro Honorarios (37 CFR 1.16)

- ☒ Solicitud provisional (\$75.00/\$150.00 Honorarios registro : \$150.00
 - ☐ Otros Honorarios (ej. Registro de Traspaso) Honorarios registro: _____
- Total de Honorarios adjuntos \$150.00

4. Forma de Pago de Honorarios

- ☒ Se adjunta cheque de la Empresa por la suma de: \$150.00
- ☐ Cobrar a Cuenta Corriente No. 13.2855 por la suma de:
Se anexa una copia de este Trámite
- ☐ No se anexa copia de trámite

Eduardo Colado

5. Por medio de la presente el Comisionado está autorizado para cobrar deficiencias en el monto adjunto o cualquier honorario adicional que se requiera durante la vigencia de esta solicitud bajo el Código de Regulaciones Federales 37 §1.16 o Código de Regulaciones Federales 37 §1.17 o bajo cualquier otra regulación aplicable (a excepción del pago de los Honorarios por emisión) a la Cuenta Corriente No. **13-2855**. Se adjunta una copia de este trámite.

Favor reembolsar cualquier sobrepago a: Marshall, O'Toole, Gersnstein, Murray & Borum a la dirección a continuación:

Favor dirigir todas las llamadas a : James Napoli a la siguiente dirección:

Atentamente,

MARSHALL, OTOOLE, GERNSTEIN, MURRAY & BORUM

6300 Sears Tower

233 South Wacker Drive

Chicago, Illinois 60606-6402

Tel: (312) 474-6300

Eduardo Calade

COINVENTORES

Expediente No. 28341/6248.2

CERTIFICADO DE CORREO POSTAL

Servicio Postal, CORREO INMEDIATO, bajo el envío número EM099777946US.

Fecha de envío: Octubre 6, 1999

Yo por el presente certifico que este documento (u honorarios), han sido enviados por Correo Certificado de Los Estados Unidos "CORREO POSTAL INMEDIATO AL DESTINATARIO" bajo el código 37 Código de Regulaciones Federales §1.10 en la fecha indicada anteriormente y rotulado a: Box Provisional Patent Application, Assistant Commissioner for patents, Washington, D.C.

Richard Zimmermann

SOLICITUD PROVISIONAL PARA CARTAS DE PATENTES
DE LOS ESTADOS UNIDOS

ESPECIFICACION

A todos aquellos a quien pueda interesar:

Informamos que nosotros , Erik H. F. Wong, ciudadano de los Estados Unidos de América, residente en 7352 Hampstead lane, portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, ciudadano de los Estados Unidos de América, residente en 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall, un ciudadano del Reino Unidos, residente en 7560 Fieldwood Circle, Mattawan Michigan,

Edwards

183

James J. Napoli (No Reg. 32, 361
Marshall, O'Toole, Gerstein, Murray & Borum
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402

60606-6402

Edwards Calado R

REIVINDICACIONES:

1. Un método que selectivamente escoge los inhibidores de norepinefrina, el método consiste del suministro de la composición a un individuo que necesite dicho tratamiento, consistiendo esta composición de selección farmacológica se serotonina (K_i)/norepinefrina (K_i) de un mínimo de 5000.

2. Un método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.1 hasta alrededor de 10 mg/día.

3. El método de acuerdo a la reivindicación 2 en el cual dicha reboxetina (S, S) se suministra aproximadamente 0.5 hasta alrededor de 8 mg/día.

4. El método de acuerdo a la Reivindicación 3 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 5mg/día.

Edwardo Calado

5. El método de acuerdo a la Reivindicación 4 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 2.5 mg/día.

6. El método de acuerdo a la Reivindicación 5 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.9 mg/día.

7. El método de acuerdo a la Reivindicación 6 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.8 mg/día.

8. El método de acuerdo a la Reivindicación 7 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.75 mg/día.

9. El método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra por vía oral, parenteral, transdermico, rectal o vaginal.

10. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra oralmente con un portador

Edwards Calles

farmacéuticamente aceptable, el cual consta de por lo menos una
 substancia aglutinante, diluyente, lubricante, agente desintegrante,
 agente efervescente, materia colorante, dulcificante y agente húmedo.

11. El método de acuerdo a la reivindicación 10 en el cual el
 suministro oral es mediante un sachet, cápsula, tableta o aerosol.

12. El método de acuerdo a la Reivindicación 9 en la cual dicha
 reboxetina (S, S) se suministra parenteralmente subcutánea,
 intravenosa o intramuscular.

13. El método de acuerdo a la Reivindicación 1, en la cual la sal
 farmacéuticamente aceptable es metanosulfonado.

14. El método de acuerdo a la Reivindicación 1 en la cual dicha
 composición consiste de reboxetina (S, S) o una sal farmacéuti-
 camente aceptable del mismo, siendo dicha composición
 substancialmente libre de (R,R) reboxetina.

15. El método de acuerdo a la Reivindicación 14 en el cual la
 reboxetina (S, S) ópticamente pura o la sal farmacéuticamente

Edwards Eladot

192
187

aceptable del mismo, consiste de aproximadamente por lo menos 90% del peso de reboxetina (S, S) e inferior aproximadamente de 10 % del peso de la Reboxetina (R,R), basado en el peso total de la reboxetina (S, S) y la reboxetina (R,R) presente.

16. El método de acuerdo a la Reivindicación 54 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, que consiste aproximadamente de por lo menos 97% del peso de reboxetina (S, S) e inferior aproximadamente de 3 % del peso de la Reboxetina (R,R), basado en el peso total de la reboxetina (S, S) y la reboxetina (R,R) presente.

17. El método de acuerdo a la Reivindicación 16 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, consiste de aproximadamente por lo menos 99% del peso de reboxetina (S, S) e inferior de alrededor de 1 % del peso de la Reboxetina (S, S), basado en el peso total de la reboxetina presente.

18. El método de acuerdo a la reivindicación 1 en el cual dicha condición es de por lo menos un trastorno adictivo y síndrome de

Edwards Calasch

abstinencia, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno de conducta, trastorno ciclotimia, depresión, trastorno distímico, fibromialgia y otros trastornos somáticos, trastorno de ansiedad generalizada, trastornos de inhalación, trastornos de intoxicación, obesidad, trastorno obsesivo -compulsivo y trastornos relacionados con el espectro, trastorno de desafío de oposición, trastorno de pánico, neuropatía periférica, trastorno de estres post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno afectivo temporal, trastorno del sueño, fobia social, trastorno de desarrollo específico y inhibidores de serotonina selectiva (SSRI), síndrome de defecarse.

19. El método de acuerdo a la reivindicación 18 en la cual los trastornos adictivos consisten de una adicción de por lo menos un alcohol, nicotina y otras sustancias psicoactivas.

20. El método de acuerdo a la reivindicación 18 en la cual los trastornos de acoplamiento constan de estado de ánimo depresivo,

Guillermo Calado

189 194

ansiedad, ansiedad combinada y estado de ánimo depresivo,
alteración en la conducta y alteraciones en la conducta combinadas
con el estado de ánimo.

21. El método de acuerdo a la reivindicación 18 en la cual los
trastornos de aprendizaje relacionados con la edad y trastornos
mentales consiste del mal de Alzheimer's.

22. El método de acuerdo a la reivindicación 18 en la cual la
depresión consiste de depresión adolescente o depresión menor.

23. El método de acuerdo a la reivindicación 18 en la cual el
trastorno disfórico premenstrual consiste del síndrome premenstrual
y trastorno disfórico en fase tardía luteal.

24. El método de acuerdo a la reivindicación 17 en la cual el
trastorno sicótico cosiste de esquizofrenia, esquizoactivo y trastorno
sicoafectivo.

25. El método de acuerdo a la reivindicación 18 en la cual la
fobia social consiste de trastorno de ansiedad social.

Edardo Calvo

26. El método de acuerdo a la reivindicación 18 en la cual el trastorno del sueño consiste de narcolepsia y enuresis.

27. El método de acuerdo a la reivindicación 18 en la cual el trastorno somático consiste de trastornos de somatización, trastorno de conversión, trastorno de dolor, hipocondría, trastorno de dismorfia corpórea, trastorno no identificado somático y somatoformas NOS.

28. El método de acuerdo a la reivindicación 18 en el cual dicha condición es de por lo menos un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, depresión, trastorno distímico, trastorno de ansiedad generalizada (GAD), adicción a la nicotina, trastorno de estrés post-traumático, trastorno disfórico premenstrual, trastorno sicótico, y (SSRI), síndrome de defecarse.

Calendo Calendo

29. El método de acuerdo a la reivindicación 28 en el cual dicha condición es por lo menos una de apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, síndrome de fatiga crónica, trastorno ciclotímico, depresión, adicción a la nicotina, trastorno de stress post-traumático, y (SSRI), síndrome de defecarse.

30. Un método de acuerdo a la reivindicación 1 en la cual el compuesto tiene una selección farmacológica de serotonina (K_i)/norepinefrina (K₁) de por lo menos aproximadamente 10,000.

31. Un método de acuerdo a la reivindicación 30 en la cual el compuesto tiene una selección farmacológica de serotonina (K_i)/norepinefrina (K₁) de por lo menos aproximadamente 12,000.

32. Un método de acuerdo a la reivindicación 31 en la cual el compuesto tiene una selección farmacológica de serotonina (K_i)/norepinefrina (K₁) de por lo menos aproximadamente 25,000.

33. Un método de acuerdo a la reivindicación 32 en la cual el compuesto tiene una selección farmacológica de serotonina (K_i)/norepinefrina (K₁) de por lo menos aproximadamente 50,000.

Edwards Calabro 1

192 197

34. Un método de acuerdo a la reivindicación 33 en la cual el compuesto tiene una selección farmacológica de serotonina (Ki)/norepinefrina (K1) de por lo menos aproximadamente 75,000.

35. Un método de acuerdo a la reivindicación 34 en la cual el compuesto tiene una selección farmacológica de serotonina (Ki)/norepinefrina (K1) de por lo menos aproximadamente 100,000.

36. Un método para el tratamiento de una condición de sufrimiento en el ser humano, o para prevenir dicha condición, en el cual el inhibidor de norepinefrina proporciona un beneficio, el método consiste en el suministro de una cantidad terapéuticamente eficaz de la composición que consta de un compuesto que tiene una selectividad farmacológica de serotonina (Ki)/norepinefrina (K1) de aproximadamente 5000.

37. Una preparación de un medicamento que consiste de un compuesto que tiene una selección farmacológica de serotonina (Ki)/norepinefrina (Ki) de aproximadamente 5000 para el tratamiento de por lo menos una condición del sistema nervioso seleccionada del grupo que consiste de los trastornos de acoplamiento,

Edwar do Calado

198
193

un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad y trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, migrañas, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno de desarrollo específico, y (SSRI), síndrome de defecarse.

38. El uso de una composición que consiste de un compuesto que tiene una selección farmacológica de serotonina (Ki)/norepinefrina (Ki) de aproximadamente 5000 para el tratamiento de por lo menos una condición del sistema nervioso seleccionada del grupo que consiste de trastornos de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno temporal

Edward Calabro
11

afectivo, trastorno de insomnio, trastorno de desarrollo específico, y
(SSRI), síndrome de defecarse.

194

Edwards Caldes

184.

20

193

PA 258499



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 06, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/158,256

FILING DATE: *October 06, 1999*



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

PROVISIONAL PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No: 28341/6248.2

PROVISIONAL PATENT APPLICATION TRANSMITTAL

Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the provisional patent application under 37 CFR 1.53(c) of

Inventors:

- | | |
|---|---|
| 1. Erik H.F. Wong,
7352 Hampstead Lane
Portage, Michigan 49024 | 4. Robert McArthur
531 Carrington Court
Kalamazoo, Michigan 49009 |
| 2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49002 | 5. Duncan P. Taylor
8722 West F Avenue
Kalamazoo, Michigan 49009 |
| 3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071 | |

Title: HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS AND METHODS OF USING THE SAME

1. Application Papers Enclosed

- | | |
|----|--|
| 1 | Title Page |
| 27 | Pages of Specification (excluding Claims & Abstract) |
| 7 | Pages of Claims |
| 1 | Page of Abstract |

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Provisional Patent Application Transmittal and the documents referred to as enclosed therewith are being deposited with the United States Postal Service on October 6, 1999, in an envelope addressed to the Assistant Commissioner for Patents, Box Provisional Patent Application, Washington, D.C. 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing Label No. EM099777946US.


Richard Zimmermann

202
197

2. **Additional Papers Enclosed**

- ☐ Declaration of Biological Deposit
- ☐ Computer readable copy of sequence listing containing nucleotide and/or amino acid sequence
- ☐ Microfiche computer program
- ☐ Verified statement(s) claiming small entity status under 37 CFR 1.9 and 1.27
- ☐ Associate power of attorney
- ☐ Verified translation of a non-English patent application
- ☐ An assignment of the invention
- ☒ Return Receipt Postcard
- ☐ Other (e.g. declaration or oath)

3. **Filing Fee Calculation (37 CFR 1.16)**

- | | | |
|---|--------------------|-----------------|
| ☒ Provisional Application (\$75.00/\$150.00) | Filing Fee: | \$150.00 |
| ☐ Other Fees (e.g. Recording Assignment) | Filing Fee: | \$_____ |
| Total Fees Enclosed | | \$150.00 |

4. **Method of Payment of Fees**

- ☒ Enclosed is our firm check in the amount of: **\$150.00**
- ☐ Charge Deposit Account No. 13-2855 in the amount of: **\$_____**
A copy of this Transmittal is enclosed.
- ☐ Not enclosed

5. **Deposit Account and Refund Authorization**

The Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees which may be required during the pendency of this application under 37 CFR 1.16 or 37 CFR 1.17 or under other applicable rules (except payment of issue fees), to Deposit Account No. 13-2855. A copy of this Transmittal is enclosed.

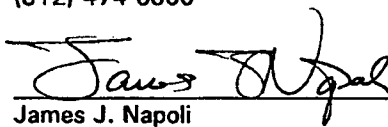
Please refund any overpayment to Marshall, O'Toole, Gerstein, Murray & Borun at the address below.

Please direct all future communications to James J. Napoli, at the address below.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

By:


James J. Napoli
Reg. No: 32,361

October 6, 1999

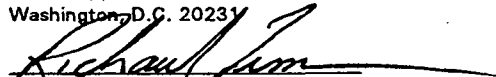
JOINT INVENTORS

Attorney Docket No. 28341/6248.2

"EXPRESS MAIL" mailing label No. EM099777946US.

Date of Deposit: October 8, 1999

I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231


Richard Zimmermann

PROVISIONAL APPLICATION FOR
UNITED STATES LETTERS PATENT

S P E C I F I C A T I O N

TO ALL WHOM IT MAY CONCERN:

Be it known that we, Erik H.F. Wong, a citizen of the United States of America, residing at 7352 Hampstead Lane, Portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, a citizen of the United States of America, residing at 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall, a citizen of the United Kingdom, residing at 7560 Fieldwood Circle, Mattawan, Michigan, 49071, Van Buren County; Robert McArthur, a citizen of the United Kingdom and Canada, residing at 531 Carrington Court, Kalamazoo, Michigan, 49009, Kalamazoo County; and Duncan P. Taylor, a citizen of the United States of America, residing at 8722 West F Avenue, Kalamazoo, Michigan, 49009, Kalamazoo County, have invented new and useful "HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS AND METHODS OF USING THE SAME," of which the following is a specification.

Attorneys for Applicants:

James J. Napoli (Reg. No. 32,361)
Marshall, O'Toole, Gerstein,
Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402

205
202

**HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE
INHIBITORS AND METHODS OF USING THE SAME**

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods of treating individuals suffering from a variety of conditions wherein inhibiting reuptake of norepinephrine provides a benefit. In particular, the present invention relates to methods of treatment comprising administration of a compound, such as (S,S) reboxetine, to an individual, wherein the compound has a high pharmacological selectivity with respect to norepinephrine reuptake sites compared to serotonin reuptake sites.

Brief Description of Related Technology

Many types of depression, mental, behavioral, and neurological disorders originate from disturbances in brain circuits that convey signals using certain monoamine neurotransmitters. Monoamine neurotransmitters include, for example, norepinephrine (noradrenaline), serotonin (5-hydroxytryptamine or 5-HT), and dopamine. Lower-than-normal levels of norepinephrine are associated with a variety of symptoms including lack of energy, motivation, and interest in life. Thus, a normal level of norepinephrine is essential to maintaining drive and capacity for reward.

These neurotransmitters travel from the terminal of a neuron across a small gap (*i.e.*, the synaptic cleft) and bind to receptor molecules on the surface of a second neuron. This binding elicits intracellular changes that initiate or activate a response or change in the postsynaptic neuron.

- 5 Inactivation occurs primarily by transport (*i.e.*, reuptake) of the neurotransmitter back into the presynaptic neuron. Abnormality in noradrenergic transmission results in various types of depression, mental, behavioral, and neurological disorders attributed to a variety of symptoms including a lack of energy, motivation, and interest in life. *See generally* R.J. Baldessarini, "Drugs and the Treatment of Psychiatric Disorders: Depression and Mania" in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, NY, NY, pp. 432-439 (1996).
- 10

- Reboxetine (*i.e.*, 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine) raises the concentration of physiologically active norepinephrine by preventing reuptake of norepinephrine, for example. Reboxetine is a norepinephrine reuptake inhibitor and has been shown to be effective in the short-term (*i.e.*, less than eight weeks) and long-term treatment of depression. In fact, reboxetine has been shown to have effectiveness that is similar to fluoxetine, imipramine, and desipramine, commonly prescribed antidepressants, in both adults and elderly patients. *See* S.A. Montgomery, *Reboxetine: Additional Benefits to the Depressed Patient*, *Psychopharmacol (Oxf)* 11:4 Suppl., S9-15 (Abstract) (1997).
- 15
- 20

- Some have divided antidepressant drugs into "generations," wherein the first generation included the monoamine oxidase inhibitors (such as isocarboxazid and phenylhydrazine) and tricyclic agents (such as imipramine). The second generation of antidepressant drugs included compounds such as mianserin and trazodone, and the third generation included drugs called selective reuptake inhibitors (*e.g.*, fluoxetine, sertraline, paroxetine, and reboxetine). The third generation antidepressants have been characterized by relatively selective action on only one of the three main monoamine systems
- 25
- 30

thought to be involved in depression (*i.e.*, 5-HT (serotonin), noradrenaline (norepinephrine), and dopamine). APP Textbook of Psychopharmacology (A.F. Schatzberg and C.B. Nemeroff), American Psychiatric Press, 2d. ed., (1998); Lexicon of Psychiatry, Neurology and the Neurosciences (F.J. Ayd, Jr.)
5 Williams and Wilkins (1995).

According to a survey by Brian E. Leonard, desipramine, maprotiline, and lofepramine are relatively selective norepinephrine reuptake inhibitors with proven efficacy. These materials increase brain noradrenaline and thereby function to relieve depression. Mianserin and mirtazepine also
10 show antidepressant-like effects by increasing noradrenaline availability by means of blocking the pre-synaptic α_2 -adrenoceptors. Still further, oxaprotiline, fezolamine, and tomoxetine are potent and selective norepinephrine reuptake inhibitors that lack neurotransmitter receptor interactions and, thus, do not cause many of the side effects characteristic of
15 classical tricyclic antidepressants. See Brian E. Leonard, "The Role of Noradrenaline in Depression: A Review," Journal of Psychopharmacology, vol. 11, no. 4 (Suppl.), pp. S39-S47 (1997)

Reboxetine also is a selective norepinephrine reuptake inhibitor, which also produces fewer of the side effects associated with the administration
20 of classical tricyclic antidepressants. The antidepressant efficacy of reboxetine is evidenced by its ability to prevent reserpine-induced blepharospasm and hypothermia in mice, down regulation of β -adrenergic receptors and desensitization of noradrenaline-coupled adenylate cyclase. See M. Brunello and G. Racagni, "Rationale for the Development of Noradrenaline Reuptake
25 Inhibitors," Human Psychopharmacology, vol. 13 (Supp.) 13-519 (1998).

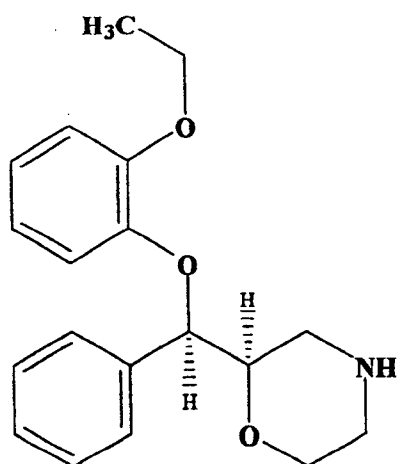
Reboxetine generally is described in Melloni *et al.* U.S. Patent Nos. 4,229,449, 5,068,433, and 5,391,735, and in GB 2,167,407, the disclosures of which are hereby incorporated by reference. Chemically, reboxetine has two chiral centers and, therefore, exists as two enantiomeric
30 pairs of diastereomers, shown below as isomers (I) through (IV):

203

(I)

203

5

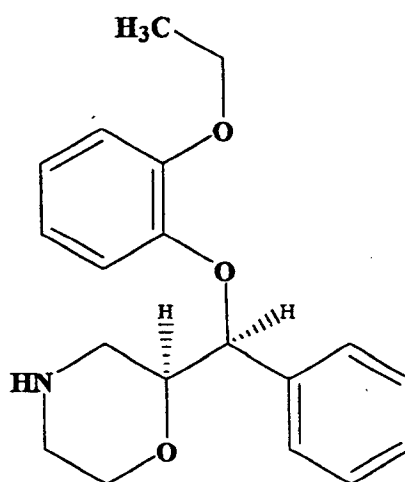


(R, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

10

(II)

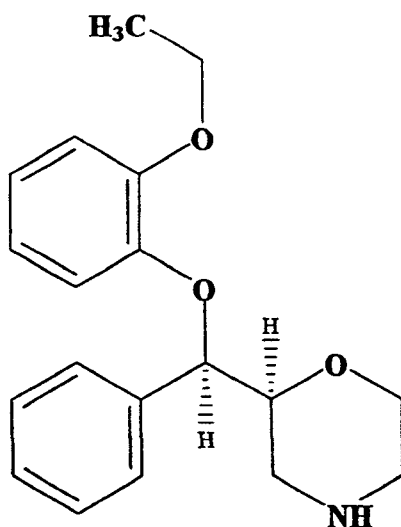
15



(S, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

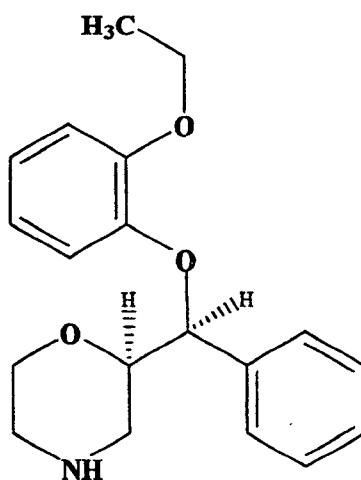
(III)

204



(R, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

(IV)



(S, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes R and S are used to denote the

205
9/2

absolute configuration of the molecule about its chiral center(s). The prefixes D and L, or (+) or (-), designate the sign of rotation of plane-polarized light by the compound, with L or (-) meaning that the compound is levorotatory. In contrast, a compound prefixed with D or (+) is dextrorotatory. There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. Thus, D-lactic acid is the same as (+)-lactic acid, and L-lactic acid is the same as (-)-lactic acid. For a given chemical structure, each of a pair of enantiomers are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric, or racemic, mixture.

Stereochemical purity is important in the pharmaceutical field, where many of the most often prescribed drugs exhibit chirality. For example, the L-enantiomer of the β -adrenergic blocking agent, propranolol, is known to be 100 times more potent than its D-enantiomer. Additionally, optical purity is important in the pharmaceutical drug field because certain isomers have been found to impart a deleterious effect, rather than an advantageous or inert effect. For example, it is believed that the D-enantiomer of thalidomide is a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, whereas its corresponding L-enantiomer is believed to be a potent teratogen.

When two chiral centers exist in one molecule, there are four possible stereoisomers: (R,R), (S,S), (R,S), and (S,R). Of these, (R,R) and (S,S) are an example of a pair of enantiomers (mirror images of each other), which typically share chemical properties and melting points just like any other enantiomeric pair. The mirror images of (R,R) and (S,S) are not, however, superimposable on (R,S) and (S,R). This relationship is called diastereoisomeric, and the (S,S) molecule is a diastereoisomer of the (R,S) molecule, whereas the (R,R) molecule is a diastereoisomer of the (S,R) molecule.

211.
265

Currently, reboxetine is commercially available only as a racemic mixture of enantiomers, (R,R) and (S,S) in a 1:1 ratio, and reference herein to the generic name "reboxetine" refers to this enantiomeric, or racemic, mixture. Reboxetine is commercially sold under the trade names of

5 EDRONAX , PROLIFT , VESTRA , and NOREBOX . As previously noted, reboxetine has been shown to be useful in the treatment of human depression. Orally administered reboxetine is readily absorbed and requires once or twice a day administration. A preferred adult daily dose is in the range of about 8 to about 10 milligrams (mg). The effective daily dosage of reboxetine for a child

10 is smaller, typically in a range of about 4 to about 5 mg. The optimum daily dosage for each patient, however, must be determined by a treating physician taking into account the patient's size, other medications which the patient may be taking, identity and severity of the particular disorder, and all of the other circumstances of the patient.

15 While reboxetine is a selective norepinephrine reuptake inhibitor, administration of reboxetine can nevertheless result in undesired side effects associated with drug-drug interactions and in other undesirable side effects such as, for example, dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in

20 males, certain anticholinergic-like effects (*e.g.*, tachyardia and urinary retention). It has been found that such side effects occur, in part, because reboxetine lacks a sufficiently high selectivity for inhibiting norepinephrine reuptake. In other words, reboxetine is blocking reuptake of other monoamines, like serotonin and dopamine, to a sufficient degree to contribute

25 to the undesired side effects.

 It has been reported that other antidepressants have a high pharmacological selectivity for inhibiting reuptake of norepinephrine. For example, oxaprotiline has a pharmacological selectivity with respect to inhibiting norepinephrine reuptake compared to serotonin reuptake of about

30 4166, based on a ratio of K_i values. The corresponding pharmacological

212
207

selectivity for desipramine is about 377, and that for maprotiline is about 446. See Elliott Richelson and Michael Pfenning, "Blockade by Antidepressants and Related Compounds of Biogenic Amine Uptake in Rat Brain Synaptosomes: Most Antidepressants Selectively Block Norepinephrine Uptake," European Journal of Pharmacology, vol. 14, pp. 277-286 (1984). Despite the relatively high selectivity of oxaprotiline, desipramine, and maprotiline, these and other known materials undesirably block receptors of other neurotransmitters to a sufficient degree that they also contribute to adverse side effects.

Accordingly, there is a need in the art for a highly selective (at one reuptake site), specific (with no activity at other receptors), and potent norepinephrine reuptake inhibitor. Furthermore, there is a need for pharmaceutical compositions containing a highly selective and potent norepinephrine reuptake inhibitor. Still further, there is a need for medicaments containing such pharmaceutical compositions, and the use of such compositions in the manufacture of such medicaments.

SUMMARY OF THE INVENTION

The present invention generally is directed to compositions and methods of treating or preventing a variety of conditions where selective, specific, and potent inhibition of norepinephrine reuptake provides a benefit.

Accordingly, one aspect of the present invention is directed to a method of selectively inhibiting reuptake of norepinephrine, the method comprising the step of administering a composition to an individual, the composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_j) of at least about 5000, preferably at least about 10,000, and more preferably at least about 12,000.

Another aspect of the present invention is directed to a method of treating a human suffering from a condition, or preventing said condition,

212
208

wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, preferably at least
5 about 10,000, and more preferably at least about 12,000.

Another aspect of the present invention is directed to a preparation of a medicament from a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, preferably at least about 10,000, and more preferably at least
10 about 12,000 to treat or prevent at least one nervous system disorder selected from the group consisting of an addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances) and withdrawal syndrome, adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of
15 conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, depression
20 (including adolescent depression and minor depression), dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder (GAD), inhalation disorders, intoxication disorders (alcohol
25 addiction), migraine headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic
30 disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and

214
209

enuresis), social phobia (including social anxiety disorder), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response).

Another aspect of the present invention is directed to use of a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, preferably at least about 10,000, and more preferably at least about 12,000, in a manufacture of a medicament to treat or prevent at least one of the aforementioned nervous system disorders.

An example of a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, is optically pure (S,S) reboxetine substantially free of its (R,R) stereoisomer. Individuals treated with optically pure (S,S) reboxetine do not experience certain adverse side effects associated with the administration of the racemic mixture of (R,R) and (S,S) reboxetine.

Optically pure (S,S) reboxetine is advantageous over prior treatment or prevention methods which utilized a racemic mixture of (R,R) and (S,S) reboxetine. In particular, it has been found that treatments using compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Therefore, norepinephrine reuptake blockage can be achieved with much lower dosages. Accordingly, the present invention may permit a substantial reduction in the customary daily dosage of a racemic mixture (*i.e.*, the commercially available reboxetine), for example, by about 50% to about 80% because of the use of an optically pure (S,S) reboxetine. In addition, treatments utilizing the optically pure (S,S) reboxetine may result in fewer undesirable adverse side effects associated with the prior treatment methods

215
210

because of the high selectivity and potency of (S,S) reboxetine with respect to inhibition of norepinephrine reuptake compared to inhibition of serotonin reuptake.

5 Additional benefits and features of the invention may become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the example and the appended claims. While the invention is susceptible of embodiments in various forms, described hereafter are specific preferred embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not
10 intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 Reboxetine is a known compound that is active on the central nervous system, and has been used as an antidepressant. Heretofore, use of reboxetine has been limited to the treatment of depression, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder. These proposed treatments are disclosed in International Publication Nos. WO 99/15163, WO 95/15176, and WO 99/15177. These treatment methods are limited to administration of a racemic mixture of the (S,S) and (R,R) reboxetine
20 stereoisomers.

Reboxetine does not act like most antidepressants. Unlike tricyclic antidepressants, and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that reboxetine is not a SSRI. Brian E. Leonard, "Noradrenaline in
25 basic models of depression." *European-Neuropsychopharmacol*, 7 Suppl. 1 pp. S11-6 and S71-3 (April 1997). Reboxetine is a selective norepinephrine reuptake inhibitor, with only marginal serotonin and no dopamine reuptake inhibitory activity. Reboxetine displays no anticholinergic binding activity in different animal models, and is substantially devoid of monoamine oxidase

216
211

(MAO) inhibitory activity. Racemic reboxetine exhibits a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of about 80. The K_i values are discussed in more detail hereafter.

5 The present invention is directed to a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, preferably at least about 10,000, and more preferably at least about 12,000. The inventive composition is useful in the treatment or prevention of diseases, disorders, and conditions (described in more detail below) wherein inhibition of reuptake of
10 norepinephrine is beneficial.

 To determine the degree of selectivity of a compound to bind to the norepinephrine reuptake site, the inhibition constant (or K_i value) of the compound for serotonin reuptake site was divided by the K_i value for norepinephrine reuptake site. A lower value of K_i for norepinephrine reuptake
15 indicates greater binding affinity to norepinephrine receptors. A higher serotonin (K_i)/norepinephrine (K_i) ratio indicates a greater selectivity for binding the norepinephrine receptor. Accordingly, the present invention is directed to a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000,
20 preferably at least about 10,000, and more preferably at least about 12,000, as noted above. Furthermore, it is envisioned that selectivity values far in excess of 12,000, such as 25,000, 50,000, 75,000, and even up to 100,000 or greater, also are beneficial.

 The compositions of the present invention, when employed in
25 effective amounts in accordance with the present invention, are selective with respect to the norepinephrine reuptake site, but do not cause significant blockade of receptors associated with undesirable side effects *e.g.*, serotonin and dopamine receptors. In other words, a dose of the inventive composition capable of inhibiting the reuptake of norepinephrine, is essentially ineffective in
30 eliciting blockade of other neurotransmitter receptors. Inhibition constants (K_i values), typically reported in units of nanamolars (nM), were calculated from

212
212

the IC₅₀ values according to the method set forth in Y.C. Cheng and W.H. Prusoff, "Relationship Between the Inhibitory Constant (K_i) and the Concentration of Inhibitor Which Causes 50% Inhibition (IC₅₀) of an Enzymatic Reaction," Biochemical Pharmacology, vol. 22, pp. 3099-3108 (1973).

5 A preferred embodiment of the inventive composition comprising the (S,S) stereoisomer of reboxetine, or a pharmaceutically acceptable salt thereof. The composition is substantially free of (R,R) reboxetine. (S,S) reboxetine has been found to be a highly selective
10 norepinephrine reuptake inhibitor and, accordingly, dose levels can be substantially reduced in comparison to racemic reboxetine. In addition, individuals treated with an optically pure (S,S) reboxetine do not experience certain adverse effects associated with the administration of the less selective and less specific racemic mixture of (R,R) and (S,S) reboxetine.

15 As used herein, the term "reboxetine" refers to the racemic mixture of the (R,R) and (S,S) enantiomers of reboxetine. In contrast, the term "(S,S) reboxetine" refers to only the (S,S) stereoisomer. Similarly, the term "(R,R) reboxetine" refers to only the (R,R) stereoisomer.

20 The phrases "optically pure (S,S) reboxetine" and "substantially free of its (R,R) stereoisomer," as used herein, mean that the composition contains a greater proportion of (S,S) reboxetine in relation to (R,R) reboxetine. In a preferred embodiment, the phrases mean that the composition is at least 90 percent by weight (wt.%) of (S,S) reboxetine, and 10 wt.% or less of (R,R) reboxetine. In a more preferred embodiment the phrases mean that
25 the composition contains at least 97 wt.% of (S,S) reboxetine, and 3 wt.% or less of (R,R) reboxetine. In an even more preferred embodiment, the phrases mean that the composition contains at least 99 wt.% of (S,S) reboxetine, and 1 wt.% or less of (R,R) reboxetine. In a most preferred embodiment, the phrases "optically pure (S,S) reboxetine" and "substantially free of its (R,R)
30 stereoisomer," as used herein, mean that the composition contains greater than 99 wt.% of (S,S) reboxetine. The foregoing percentages are based upon the

total amount of (R,R) and (S,S) reboxetine present in the composition. The phrases "substantially free of (R,R) reboxetine," "substantially optically pure (S,S) stereoisomer of reboxetine," "substantially optically pure (S,S) reboxetine," "optically pure (S,S) stereoisomer of reboxetine," and "optically pure (S,S) reboxetine" are also encompassed by the above-described amounts.

The phrases "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases. Because the active compound (*e.g.*, (S,S) reboxetine) used in the present invention can be basic, salts may be prepared from pharmaceutically acceptable acids. Suitable pharmaceutically acceptable acids include acetic, benzenesulfonic (besylate), benzoic, p-bromophenylsulfonic, camphorsulfonic, carbonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, isethionic, lactic, maleic, malic, mandelic, methanesulfonic (mesylate), mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. Examples of such pharmaceutically acceptable salts of (S,S) reboxetine, thus, include, but are not limited to, acetate, benzoate, β -hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, and the like. A preferred pharmaceutical salt of (S,S) reboxetine is methanesulfonate (*i.e.*, mesylate), which is prepared using methanesulfonic acid.

The phrases "side effects," adverse effects," and "adverse side effects" in relation to norepinephrine reuptake inhibitors include, but are not

214

limited to, dizziness, insomnia, lightheadedness, changes in blood pressure, gastrointestinal disturbances, sexual dysfunction in males, extrapyramidal side effects, certain anticholinergic-like effects (*e.g.*, tachycardia, blurred vision), and undesired side effects associated with drug-drug interactions.

5 Another embodiment of the present invention includes a method of selectively inhibiting reuptake of norepinephrine, the method comprising the step of administering a composition to an individual, the composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, preferably at least about 10,000, and more preferably at least about 12,000.

10 As used herein, the terms "treat," "treatment," and "treating," refer to: (a) preventing a disease, disorder, or condition from occurring in a human which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (b) inhibiting the disease, disorder, or condition, *i.e.*, arresting its development; and (c) relieving the disease, disorder, or condition, *i.e.*, causing regression of the disease, disorder and/or condition. For the sake of simplicity, the term "conditions" as used hereinafter encompasses conditions, diseases, and disorders.

15 Methods and compositions of the present invention are useful in treating a human condition wherein inhibiting reuptake of norepinephrine provides a benefit. The method comprises the step of administering, and preferably orally administering, a sufficient amount of the inventive composition to provide a total dose of about 0.1 to about 10 mg/day of the selective compound to an individual.

20 More specifically, administration of the inventive composition is effective in treating depression. Depression is often associated with other diseases or conditions, or is caused by such other conditions. For example, depression is often associated with Parkinson's disease, HIV, Alzheimer's disease, and with the abuse of anabolic steroids. Depression also is associated with the abuse of many substances, or may be associated with the behavioral problems resulting from or occurring in combination with head injuries, mental

retardation, and stroke. Depression in all its variations is but one target of treatment utilizing the inventive compositions.

5 The inventive composition also is useful for treating many other conditions including, but not limited to, addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances) and withdrawal syndrome, adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other
10 cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, depression (including adolescent depression and minor depression), dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized
15 anxiety disorder (GAD), inhalation disorders, intoxication disorders (alcohol addiction), migraine headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), specific
25 developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial satisfactory response).

30 Reference to treatments for "nicotine addiction" herein also includes treatments for smoking cessation. Many of the foregoing human diseases, disorders, and conditions are generally described by the American

22
212

commercially-available reboxetine is a racemic mixture of the (R,R) and (S,S) enantiomers of 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine. It has now been discovered that the (S,S) stereoisomer is the most active and the most selective of the reboxetine stereoisomers with respect to inhibiting the reuptake of norepinephrine. In addition, when administered to an individual, in the dosages described herein, as an optically pure material (*i.e.*, in the substantial absence of its (R,R) diastereomer), the individual does not experience many of the adverse side effects associated with the administration of commercially-available reboxetine. Furthermore, it has further been discovered that the (S,S) and (R,R) enantiomers have a reversed selectivity for the norepinephrine neurotransmitter in relation to the serotonin neurotransmitter, and an optically pure (S,S) reboxetine is significantly more effective at inhibiting reuptake of norepinephrine than either the (R,R) enantiomer or a racemic mixture of the (S,S) and (R,R) enantiomers.

Specifically, it has been found that compositions containing optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Accordingly, the typical daily dosage of the racemic mixture (*i.e.*, commercially available reboxetine) can be reduced by about 50% to about 80% when using an optically pure (S,S) reboxetine. The reduction in dosage does not lead to a reduction in efficacy, but the reduction or elimination of various adverse side effects was observed.

In particular, because optically pure (S,S) reboxetine is highly selective with respect to inhibiting norepinephrine reuptake compared to serotonin reuptake, adverse side effects associated with serotonin reuptake are reduced or eliminated. Such adverse side effects include, but are not limited to, gastrointestinal disturbances, anxiety, sexual dysfunction, and undesirable side effects associated with drug-drug interactions.

The synthesis of a racemic mixture of reboxetine is disclosed in Melloni *et al.* U.S. Patent No. 4,229,449. Individual stereoisomers of reboxetine can be obtained by resolution of the racemic mixture of enantiomers

723
213

using conventional methods generally known by those skilled in the art. Such methods include, but are not limited to, resolution by simple crystallization and chromatographic techniques, for example, as set forth in GB 2,167,407.

While it is possible to administer a highly selective
5 norepinephrine reuptake inhibitor directly without any formulation, a composition preferably is administered in the form of pharmaceutical medicaments comprising the selective norepinephrine reuptake inhibitor. The inventive composition can be administered in oral unit dosage forms such as tablets, capsules, pills, powders, or granules. The inventive composition also
10 can be introduced parenterally, (e.g., subcutaneously, intravenously, or intramuscularly), using forms known in the pharmaceutical art. The inventive composition further can be administered rectally or vaginally in such forms as suppositories or bougies. The inventive composition also can be administered topically or transdermally, such as with a "patch" containing active ingredient.
15 Transdermal delivery patches can be used to provide continuous, pulsatile, or on-demand infusion of the inventive compositions in controlled amounts. The construction and use of transdermal delivery patches are well known in the pharmaceutical art, and are described, for example, in U.S. Patent Nos. 3,742,951, 3,742,951, 3,797,494, 3,996,934, 4,031,894, and 5,023,252.

20 It may be desirable or necessary to introduce the inventive composition or pharmaceutical compositions containing the selective norepinephrine reuptake inhibitor to the brain, either directly or indirectly. Direct techniques usually involve placement of a suitable drug delivery catheter into the ventricular system to bypass the blood-brain barrier. One such suitable
25 delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent No. 5,011,472, the disclosure of which is incorporated herein by reference.

In general, the preferred route of administering the inventive composition is oral, with a once or twice a day administration. The dosage
30 regimen and amount for treating patients with the inventive composition is selected in accordance with a variety of factors including, for example, the

224
219

type, age, weight, sex, and medical condition of the patient, the severity of the condition, the route of administration and the particular compound employed, either racemate or pure enantiomer. An ordinarily skilled physician or psychiatrist can readily determine and prescribe an effective (*i.e.*, therapeutic) amount of the compound to prevent or arrest the progress of the condition. In so proceeding, the physician or psychiatrist could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained.

Pharmaceutical compositions suitable for oral administration can be of any convenient form, such as sachets, tablets, capsules, pills, or aerosol sprays, each containing a predetermined amount of the active compound either as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions can be prepared by any method that includes the step of bringing the active compound either into intimate association with a carrier, which constitutes one or more necessary or desirable ingredients. Generally, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into a desired form.

For example, a tablet can be prepared by compression or molding techniques, optionally, using one or more accessory ingredients. Compressed tablets can be prepared by compressing the active ingredient in a suitable machine into a free-flowing form, such as a powder or granules. Thereafter, the compressed, free-flowing form optionally can be mixed with binders, diluents, lubricants, disintegrating agents, effervescent agents, dyestuffs, sweeteners, wetting agents, and non-toxic and pharmacologically inactive substances typically present in pharmaceutical compositions. Molded tablets can be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine.

Suitable binders for use in the pharmaceutical preparation include, for example, starches, gelatin, methylcellulose, gum arabic, tragacanth,

and polyvinylpyrrolidone. Suitable diluents for use in the pharmaceutical preparation include, for example, lactose, dextrose, sucrose, mannitol, sorbitol, and cellulose. Suitable lubricants for use in the pharmaceutical preparation include, for example, silica, talc, stearic acid, magnesium or calcium stearate, and or polyethylene glycols. Suitable disintegrating agents for use in the pharmaceutical preparation include, for example, starches, alginic acid, and alginates. Suitable wetting agents for use in the pharmaceutical preparation include, for example, lecithin, polysorbates, and laurylsulfates. Generally, any effervescing agents, dyestuffs, and/or sweeteners known by those of ordinary skill in the art can be used in the preparation of a pharmaceutical composition.

The pharmacological activities described above provide a basis for the pharmacological utility of the inventive composition. The activity of the inventive composition in the inhibition of the reuptake of norepinephrine provides a method of selectively inhibiting the reuptake of norepinephrine comprising administering an effective amount of the selective norepinephrine reuptake inhibitor to an individual. As described above, numerous physiological and psychological benefits can be obtained through the therapeutic administration of drugs which selectively inhibit the reuptake of norepinephrine. Such drugs increase the level of norepinephrine (an endogenous monoamine) by inhibiting the neuronal mechanism for recovering norepinephrine from the synapse without interfering with other neuronal receptors including, but not limited to, serotonin, dopamine, histaminergic, β -adrenergic, muscarinic, and cholinergic receptors. Compositions of the present invention are highly selective for norepinephrine and, therefore, minimize or eliminate undesired side-effects associated with the therapeutic administration of non-selective inhibitors.

A "therapeutically effective amount" of the inventive composition generally refers to an amount of the composition sufficient to treat one of the aforementioned conditions at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutically effective amount of the inventive composition suitable for the selective inhibition of norepinephrine

226

221

reuptake can be determined by a treating physician or psychiatrist. Desirably, a daily dose of the inventive composition (*e.g.*, tablet, sachet, or capsule) contains about 0.1 to about 10 mg of the highly selective norepinephrine reuptake inhibitor. For example, a daily dose can contain about 0.1 to about 10 mg of optically pure (S,S) reboxetine. More preferably, each dose of the composition contains about 0.5 to about 8 mg of the active ingredient, the highly selective norepinephrine reuptake inhibitor. Even more preferably, however, each dose contains from about 0.5 to about 5 mg of the active ingredient. This dosage form permits the full daily dosage of about 0.5 to about 2.5 mg to be administered in one or two oral doses. This will allow for tablets containing 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5 mg of the highly selective norepinephrine reuptake inhibitor, *e.g.*, optically pure (S,S) reboxetine that is substantially free of its (R,R) stereoisomer.

In another embodiment, a preferred daily dose of the inventive composition (*e.g.*, tablet, sachet, or capsule) contains about 0.1 to about 0.9 mg of the highly selective norepinephrine reuptake inhibitor. For example, a daily dose can contain about 0.1 to about 0.9 mg of optically pure (S,S) reboxetine. More preferably, each dose of the composition contains about 0.5 to about 0.8 mg of the active, highly selective norepinephrine reuptake inhibitor. Even more preferably, however, each dose contains from about 0.5 to about 0.75 mg of the active ingredient. This dosage form permits the full daily dosage of about 0.5 to about 0.9 mg to be administered in one oral dose.

Patients suffering from, for example, depression, nicotine addiction, conduct disorder, oppositional defiant disorder, and/or attention-deficit hyperactivity disorder will benefit from the administration of the inventive composition regardless of these or other co-morbid conditions. Diagnostic criteria for these disorders generally are provided by the American Psychiatric Association and published in their "Diagnostic and Statistical Manual of Mental Disorders," 4th ed. rev. (Washington D.C. 1994), and in

227
220

International Publication Nos. WO 99/15177, WO 99/15176, and WO 99/15163, the disclosures of which are hereby incorporated by reference.

Furthermore, patients suffering from addictive disorders and withdrawal syndromes, adjustment disorders, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, bulimia nervosa, chronic fatigue, depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine addiction, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, schizoaffective disorder, and SSRI "poop out" syndrome also will benefit from the administration of the inventive composition.

The aforementioned conditions display similar patterns in children, adolescents, and adults. Hence, methods and compositions of the present invention are effective in the treatment of child, adolescent, and adult patients. For purposes of the present invention, a child is considered to be a person below the age of puberty, an adolescent is considered to be a person between the age of puberty and up to about 18 years of age, and an adult generally is a person of at least about 18 years of age. As previously noted, the optimum daily dosage for each patient should be determined by a treating physician or psychiatrist taking into account each patient's size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient.

Other desirable characteristics of the highly selective and potent norepinephrine reuptake inhibitor according to the present invention include, but are not limited to, that it (a) is a highly potent, pharmacologically specific, and fast acting agent; (b) has potent antireserpine activity, and combines the inhibitory properties of classical tricyclic antidepressants on the reuptake of noradrenaline with an ability to desensitize β -adrenergic receptor function, without showing any appreciable blocking action at muscarinic, cholinergic, histaminergic, and α -adrenergic receptors; and, (c) exhibits less receptor interactions than tricyclic antidepressants; (d) exhibits no evidence of

cardiotoxicity; and (e) exhibits no drug-drug interactions observed with some selective serotonin reuptake inhibitors.

EXAMPLE

5 This example demonstrates the superior pharmacological selectivity and potency of a composition according to the present invention. More specifically, this example demonstrates the superior pharmacological selectivity and potency of (S,S) reboxetine compared to its (R,R) stereoisomer and to racemic reboxetine.

10 Sprague-Dawley rats weighing about 250 to about 300 grams (g) were decapitated, and cerebral cortical tissue was removed immediately. Cerebral cortices were homogenized in nine volumes of medium each containing 0.32 molar (M) sucrose using a rotating pestle. The obtained homogenate was centrifuged at about 1000 x g for about 10 minutes at about
15 4°C. A supernatant was collected and further centrifuged at about 20,000 x g for about 20 minutes at a temperature of about 4°C. A protein pellet resulting from the centrifuge steps was re-suspended in a Kreb's-Hepes buffer to result in a protein concentration of about 2 mg/ml of buffer. The buffer was maintained at a pH of about 7.0 and contained: 20 mM Hepes; 4.16 mM
20 NaHCO₃; 0.44 mM KH₂PO₄; 0.63 mM NaH₂PO₄; 127 mM NaCl; 5.36 mM KCl; 1.26 mM CaCl₂; and 0.98 mM MgCl₂.

Protein/buffer suspension was introduced into 166 assay tubes such that about 30 µg (10⁻⁶ grams) to about 150 µg of the protein was added to each of 166 assay tubes (*i.e.*, 80 assays per transporter assay). Binding to
25 serotonin and norepinephrine reuptake sites was determined as follows. Synaptosomal uptake of ³H-norpinephrine was determined as follows. About 1.4 nanomolar of [³H]citalopram and about 1.9 nM of [³H]nisoxetine were used to label serotonin and norepinephrine reuptake sites, respectively. Nonspecific binding was defined by 100 micromolar (µM) fluoxetine (for serotonin) and 10
30 µM desipramine (for norepinephrine). Incubation in total assay volume of

about 500 microliters (μl) was carried out for about 60 minutes (for serotonin) and 120 minutes (for norepinephrine). Both incubations were carried out at about 25°C, and terminated by rapid filtration through a 48-well cell harvester though GFB filters (pre-soaked with about 0.5 PEI for about 4 hours) in a 3 x 5 ml of ice-cold 200 mM tris-HCl, pH 7.0. Punched-out filters were placed into 7 ml minivials and radioactive assayed by liquid scintillation counting.

The ability of reboxetine (*i.e.*, racemic mixture of (R,R) and (S,S) reboxetine), (R,R) reboxetine, and (S,S) reboxetine to bind to norepinephrine and serotonin reuptake sites was evaluated in binding assays using the two radioligands, [³H]citalopram and [³H]nisoxetine. The concentration of the test compound required to inhibit 50% of the specific binding at the two reuptake sites (IC₅₀ values) were determined by non-linear least square regression analysis. A conversion of IC₅₀ values to K_i values was performed using the Cheng-Prassoff equation presented below:

$$K_i = IC_{50} / (1 + ([L] / [K_d \text{ of } L]))$$

wherein [L] is the radioligand concentration used in nM, and K_d is the binding affinity of L in nM. See Y.C. Cheng and W.H. Prusoff, "Relationship Between the Inhibitory Constant (K_i) and the Concentration of Inhibitor Which Causes 50% Inhibition (IC₅₀) of an Enzymatic Reaction," Biochemical Pharmacology, vol. 22, pp. 3099-3108 (1973).

The K_i values calculated according to the Cheng-Prassoff equation are provided in the table below:

Table			
Compound	Norepinephrine Reuptake (K _i nM)	Serotonin Reuptake (K _i nM)	Selectivity of K _i of Serotonin/Norepinphrine
(S,S) Reboxetine	0.23 ± 0.06	2937 ± 246	12,770
(R,R) Reboxetine	7.0 ± 1.7	104 ± 43	15
Reboxetine	1.6 ± 0.6	129 ± 13	81

The data shows that (S,S) reboxetine is about five to about eight fold more potent than the reboxetine racemate with respect to inhibiting the reuptake of norepinephrine. In addition, racemic reboxetine has an 81 fold selectivity favoring norepinephrine reuptake inhibition over serotonin reuptake inhibition. Unexpectedly, the enantiomeric selectivity of the (S,S) and (R,R) reboxetine stereoisomers with respect to inhibiting the reuptake of norepinephrine and serotonin are quite different. The (S,S) enantiomer is very poor with respect to inhibiting reuptake of serotonin (*i.e.*, a high K_i) and, therefore, has a surprisingly high selectivity for the norepinephrine reuptake site. In particular, the selectivity of serotonin versus norepinephrine increases from 81 (for the racemate) to 12,770 for an optically pure (S,S) reboxetine. Accordingly, administration of a therapeutic dose of (S,S) reboxetine effectively inhibits norepinephrine reuptake, but serotonin reuptake essentially is not affected. Likewise, there is a further increase in separation between the action on norepinephrine reuptake sites and at other receptors. As a consequence, adverse side effects associated with the inhibition of serotonin reuptake and blockade at other receptors are not manifested.

Surprisingly, this effect is not observed with (R,R) reboxetine, but are quite to the contrary. (R,R) reboxetine is a weaker inhibitor than (S,S) reboxetine with respect to norepinephrine reuptake, *i.e.*, affinity (K_i) for (R,R) reboxetine is 7 nM whereas the K_i for (S,S) reboxetine is 0.23 nM. In addition, (R,R) reboxetine is much more effective at inhibiting serotonin uptake than (S,S) reboxetine, *i.e.*, K_i for (R,R) reboxetine is 104 nM, whereas the K_i for (S,S) reboxetine is 2937 nM. Accordingly, (R,R) reboxetine has a low selectivity for norepinephrine reuptake inhibition versus serotonin reuptake inhibition.

The surprisingly high potency of the (S,S) enantiomer over both the racemic reboxetine and (R,R) reboxetine provides a treating physician an ability to prescribe an effective dosage of a norepinephrine reuptake inhibitor, *i.e.*, (S,S) reboxetine, that is about 10% to about 20% of the current daily

223

dosage of reboxetine (racemate) to achieve the same reuptake inhibition at the norepinephrine site. In addition, the surprisingly high inhibition selectivity of an optically pure (S,S) reboxetine essentially limits inhibition to norepinephrine reuptake, thereby reducing adverse side effects associated with inhibition at serotonin reuptake sites and blockade at other receptors.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

What is claimed is:

232

227

1. A method of selectively inhibiting reuptake of norepinephrine, the method comprising the step of administering a composition to an individual, the composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000.

2. The method of claim 1 wherein said composition is administered in an amount of about 0.1 to about 10 mg/day.

3. The method of claim 2 wherein said composition is administered in an amount of about 0.5 to about 8 mg/day.

4. The method of claim 3 wherein said composition is administered in an amount of about 0.5 to about 5 mg/day.

5. The method of claim 4 wherein said composition is administered in an amount of about 0.5 to about 2.5 mg/day.

6. The method of claim 5 wherein said composition is administered in an amount of about 0.5 to about 0.9 mg/day.

7. The method of claim 6 wherein said composition is administered in an amount of about 0.5 to about 0.8 mg/day.

8. The method of claim 7 wherein said composition is administered in an amount of about 0.5 to about 0.75 mg/day.

9. The method of claim 1 wherein said composition is administered orally, topically, parenterally, transdermally, rectally, or vaginally.

233
228

10. The method of claim 9 wherein said composition is orally administered with a pharmaceutically acceptable carrier comprising at least one of a binder, diluent, lubricant, disintegrating agent, effervescing agent, dyestuff, sweetener, and wetting agent.

11. The method of claim 10 wherein the oral administration is by a sachet, capsule, tablet, or aerosol spray.

12. The method of claim 9 wherein said composition is parenterally administered subcutaneously, intravenously, or intramuscularly.

13. The method of claim 1 wherein the pharmaceutically acceptable salt is methanesulfonate.

14. The method of claim 1 wherein said composition comprises an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, said composition being substantially free of (R,R) reboxetine.

15. The method of claim 14 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 90 wt.% of (S,S) reboxetine, and less than about 10 wt.% of (R,R) reboxetine, based on the total weight of the (S,S) and (R,R) reboxetine present.

16. The method of claim 15 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 97 wt.% of (S,S) reboxetine and less than about 3 wt.% of (R,R) reboxetine, based on the total weight of the (S,S) and (R,R) reboxetine present.

229

17. The method of claim 16 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 99 wt.% of (S,S) reboxetine and less than about 1 wt.% of (R,R) reboxetine, based on the total weight of the (S,S) and (R,R) reboxetine present.

18. The method of claim 1 wherein said condition is at least one of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

19. The method of claim 18 wherein the addictive disorder comprises an addiction to at least one of alcohol, nicotine, and other psychoactive substances.

20. The method of claim 18 wherein the adjustment disorder comprises depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood.

21. The method of claim 18 wherein the age-associated learning and mental disorder comprises Alzheimer's disease.

235
230

22. The method of claim 18 wherein the depression comprises adolescent depression and minor depression.

23. The method of claim 18 wherein the premenstrual dysphoric disorder comprises premenstrual syndrome and late luteal phase dysphoric disorder.

24. The method of claim 18 wherein the psychotic disorder comprises schizophrenia, schizoaffective and schizophreniform disorders.

25. The method of claim 18 wherein social phobia comprises social anxiety disorder.

26. The method of claim 18 wherein the sleep disorder comprises narcolepsy and enuresis.

27. The method of claim 18 wherein somatoform disorders comprise somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS.

28. The method of claim 18 wherein said condition is at least one of an adjustment disorder, an age-associated learning or mental disorder, apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, bulimia nervosa, chronic fatigue, cyclothymic disorder, depression, dysthymic disorder, generalized anxiety disorder, nicotine addiction, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, and SSRI "poop out" syndrome.

29. The method of claim 28 wherein said condition is at least one of apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, chronic fatigue, cyclothymic disorder, depression, nicotine addiction, post-traumatic stress disorder, and SSRI "poop out" syndrome.

30. The method of claim 1 wherein the compound has a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 10,000.

31. The method of claim 30 wherein the compound has a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 12,000.

32. The method of claim 31 wherein the compound has a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 25,000.

33. The method of claim 32 wherein the compound has a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 50,000.

34. The method of claim 33 wherein the compound has a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 75,000.

35. The method of claim 34 wherein the compound has a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 100,000.

231
250

36. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000.

37. A preparation of a medicament from a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000 to treat or prevent at least one nervous system condition selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

238
233

38. Use of a composition comprising a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000 in a manufacture of a medicament to treat or prevent at least one nervous system condition selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

234

1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398</
------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	--------

Junio 30, 2000
Traducción Oficial No.0283
REF:PHARMACIA & UPJOHN CO.
Patente No.60/170,381

(Pharmacia & Upjohn)
Caso-28341/62484

235

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
OFICINA DE MARCAS Y PATENTES

Junio 06, 2000

Por medio del presente documento se certifica que adjunta se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud: 60/170,381

Fecha de Registro:Diciembre 13, 1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma: P. SWAIN

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes realizado de color dorado.

Eduardo

236

HOJA DE SOLICITUD PROVISIONAL
EN LA OFICINA DE MARCAS Y PATENTES DE LOS
ESTADOS UNIDOS

Expediente No. : 28341/6248.3

TRAMITE DE PATENTE PARA SOLICITUD PROVISIONAL

Correo:
Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Estimados Señores:

Por medio de la presente solicitamos una Patente Provisional bajo el Código 37 de
Regulaciones Federales § 1.53 (c) de los siguientes inventores:

1. Erik H. F. Wong
7352 Hampstead Lane
Portage, Michigan 49024
2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49002
3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071

Eduardo Calado R.

4. Robert MacArthur
531 Carrington Court
Kalamazoo, Michigan 49009

5. Duncan P. Taylor
8722 West F. Avenue
Kalamazoo, Michigan 49009

Titulo: INHIBIDORES ALTAMENTE SELECCIONADOS PARA LA
REASIMILACION DE LA NOREPINEFRINA Y METODOS UTILIZANDO LOS
MISMOS

1. PARTES DE LA SOLICITUD INCLUIDAS

- 1 Título
- 26 Páginas de especificaciones (no incluyendo Reivindicaciones y resumen)
- 7 Páginas de reivindicaciones
- 1 Página resumen

CERTIFICADO DE CORREO POSTAL (37 CFR 1.10)

Yo, por medio del presente documento certifico que, el trámite provisional de patente y los documentos que hacen referencia a la misma, han sido enviados por Correo Certificado de Los Estados Unidos en la fecha Diciembre 13, 1999 en un sobre rotulado al Comisionado Asistente para Patentes, Box Provisional Patent Application, Washington, DC., 20231. mediante el Servicio de Correo Certificado al Destinatario del Servicio Postal de los Estados Unidos, bajo el envío número EM099776733US.

Firma: Richard Zimmermann

Eduardo Caludo
Eduardo Caludo
Inventor

244
238

Documentos adicionales Adjuntos

- ☐ Certificado de Deposito Biológico
- ☐ Un disco que contiene nucleotidos y/o secuencia de amino ácidos en formato legible por computadora.
- ☐ Programa de Computadora Microficha
- ☐ Declaraciones verificadas de reivindicaciones de estatus de Pequeña empresa bajo el Código de Regulaciones Federales 1.9 y 1.27
- ☐ Poder
- ☐ Traducción Oficial de solicitudes de patente en otro idioma aparte del inglés.
- ☐ Transferencia del Invento
- ☒ Sobre con timbre prepago
- ☐ Otros Honorarios (ej. copia juramentada)

3. Cálculo de Registro Honorarios (37 CFR 1.16)

- ☒ Solicitud provisional (\$75.00/\$150.00 Honorarios registro : \$150.00
 - ☐ Otros Honorarios (ej. Registro de Traspaso) Honorarios registro: _____
- Total de Honorarios adjuntos \$150.00

4. Forma de Pago de Honorarios

- ☒ Se adjunta cheque de la Empresa por la suma de: \$150.00
 - ☐ Cobrar a Cuenta Corriente No. 13.2855 por la suma de: _____
- Se anexa una copia de este Trámite
-
- ☐ No se anexa copia de trámite

5. Por medio de la presente el Comisionado está autorizado para cobrar deficiencias en el monto adjunto o cualquier honorario adicional que se requiera durante la vigencia de

Eduardo Calado

esta solicitud bajo el Código de Regulaciones Federales 37 §1.16 o Código de Regulaciones Federales 37 §1.17 o bajo cualquier otra regulación aplicable (a excepción del pago de los Honorarios por emisión) a la Cuenta Corriente No. **13-2855**. Se adjunta una copia de este trámite.

Favor reembolsar cualquier sobrepago a: Marshall, O'Toole, Gersnstein, Murray & Borum a la dirección a continuación:

Favor dirigir todas las llamadas a : James Napoli a la siguiente dirección:

Atentamente,

MARSHALL, OTOOLE, GERNSTEIN, MURRAY & BORUM

6300 Sears Tower

233 South Wacker Drive

Chicago, Illinois 60606-6402

Tel: (312) 474-6300

Edmundo Calles N.

COINVENTORES

Expediente No. 28341/6248.3

CERTIFICADO DE CORREO POSTAL

Servicio Postal, CORREO INMEDIATO, bajo el envío número EM099776733US.

Fecha de envío: Diciembre 13, 1999

Yo por el presente certifico que este documento (u honorarios), han sido enviados por Correo Certificado de Los Estados Unidos "CORREO POSTAL INMEDIATO AL DESTINATARIO" bajo el código 37 Código de Regulaciones Federales §1.10 en la fecha indicada anteriormente y rotulado a: Box Provisional Patent Application, Assistant Commissioner for patents, Washington, D.C.20231

Richard Zimmermann

Hay firma de Richard Zimmermann.

SOLICITUD PROVISIONAL PARA CARTAS DE PATENTES
DE LOS ESTADOS UNIDOS

ESPECIFICACION

A todos aquellos a quien pueda interesar:

Informamos que nosotros, Erik H. F. Wong, ciudadano de los Estados Unidos de América, residente en 7352 Hampstead lane, portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, ciudadano de los Estados Unidos de América, residente en 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall, un ciudadano del Reino Unido, residente en 7560 Fieldwood Circle, Mattawan, Michigan,

Edwards Palacios

241

James J. Napoli (No Reg. 32, 361
Marshall, O'Toole, Gerstein, Murray & Borum
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402

Eduardo Calandak

REIVINDICACIONES:

1. Un método para tratar el sufrimiento humano de una condición, en el cual los inhibidores de norepinefrina proporcionan un beneficio; el método consiste en el suministro de una cantidad terapéuticamente eficaz de una reboxetina ópticamente pura (S,S), o una sal farmacéuticamente aceptable de la misma, aplicandosele a un paciente que necesite el mencionado tratamiento, y siendo esta dicha reboxetina ópticamente pura (S, S) substancialmente libre de reboxetina (R, R).

2. Un método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.1 hasta alrededor de 10 mg/día.

3. El método de acuerdo a la reivindicación 2 en el cual dicha reboxetina (S, S) se suministra aproximadamente 0.5 hasta alrededor de 8 mg/día.

Eduardo Calado

243 . 249

4. El método de acuerdo a la Reivindicación 3 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 5mg/día.

5. El método de acuerdo a la Reivindicación 4 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 2.5 mg/día.

6. El método de acuerdo a la Reivindicación 5 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.9 mg/día.

7. El método de acuerdo a la Reivindicación 6 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.8 mg/día.

8. El método de acuerdo a la Reivindicación 7 en la cual dicha reboxetina (S, S) se suministra en una cantidad aproximada de 0.5 hasta alrededor 0.75 mg/día.

Eduardo Celado

9. El método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) se suministra por vía oral, parenteral, transdermico,rectal o vaginal.

10. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra oralmente con un portador farmacéuticamente aceptable, el cual consta de por lo menos una substancia aglutinante, diluyente, lubricante, agente desintegrante, agente efervescente, materia colorante, dulcificante y agente húmedo.

11. El método de acuerdo a la reivindicación 10 en el cual el suministro oral es mediante un sachet, cápsula, tableta o aerosol.

12. El método de acuerdo a la Reivindicación 9 en la cual dicha reboxetina (S, S) se suministra parenteralmente subcutánea, intravenosa o intramuscular.

13. El método de acuerdo a la Reivindicación 1, en la cual la sal farmacéuticamente aceptable es metanosulfonado.

14. El método de acuerdo a la Reivindicación 1 en la cual dicha reboxetina (S, S) o sal farmacéuticamente aceptable del mismo,

Edwards Calado

245 ~~24~~

consiste de aproximadamente 90% de peso de la reboxetina (S,S) o inferior de alrededor 10% del peso de la reboxetina (S, S) basado en el peso total de la reboxetina presente.

15. El método de acuerdo a la Reivindicación 14 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, consiste de aproximadamente por lo menos 97% del peso de reboxetina (S, S) e inferior de alrededor de 3 % del peso de la Reboxetina (S, S), basado en el peso total de la reboxetina presente.

16. El método de acuerdo a la Reivindicación 15 en el cual la reboxetina (S, S) ópticamente pura o la sal farmacéuticamente aceptable del mismo, consiste de aproximadamente por lo menos 99% del peso de reboxetina (S, S) e inferior de alrededor de 1 % del peso de la Reboxetina (S, S), basado en el peso total de la reboxetina presente.

17. El método de acuerdo a la reivindicación 1 en el cual dicha condición es de por lo menos un trastorno adictivo y síndrome de abstinencia, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía,

Eduardo Calado

trastorno por déficit de atención debido a condiciones generales
 médicas, trastorno de déficit de atención por hiperactividad,
 trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica,
 trastorno de conducta, trastorno ciclotimia, depresión, trastorno
 distímico, fibromialgia y otros trastornos somáticos, trastorno de
 ansiedad generalizada, trastornos de inhalación, trastornos de
 intoxicación, obesidad, trastorno obsesivo -compulsivo y trastornos
 relacionados con el espectro, trastorno de desafío de oposición,
 trastorno de pánico, neuropatía periférica, trastorno de estres post-
 traumático, trastorno disfórico premenstrual, trastorno sicótico,
 trastorno afectivo temporal, trastorno del sueño, fobia social,
 trastorno de desarrollo específico y inhibidores de serotonina
 selectiva (SSRI), síndrome de defecarse.

18. El método de acuerdo a la reivindicación 17 en la cual los
 trastornos adictivos consisten de una adicción de por lo menos un
 alcohol, nicotina y otras sustancias psicoactivas.

19. El método de acuerdo a la reivindicación 17 en la cual los
 trastornos de acoplamiento constan de estado de ánimo depresivo,
 ansiedad, ansiedad combinada y estado de ánimo depresivo,

Edwardo Calado

247 250

alteración en la conducta y alteraciones en la conducta combinadas con el estado de ánimo.

20. El método de acuerdo a la reivindicación 17 en la cual los trastornos de aprendizaje relacionados con la edad y trastornos mentales consiste del mal de Alzheimer's.

21. El método de acuerdo a la reivindicación 17 en la cual la depresión consiste de depresión adolescente o depresión menor.

22. El método de acuerdo a la reivindicación 17 en la cual el trastorno disfórico premenstrual consiste del síndrome premenstrual y trastorno disfórico en fase tardía luteal.

23. El método de acuerdo a la reivindicación 17 en la cual el trastorno sicótico cosiste de esquizofrenia, esquizoactivo y trastorno sicoafectivo.

24. El método de acuerdo a la reivindicación 17 en la cual la fobia social consiste de trastorno de ansiedad social.

Edwards Calado

248 231

25. El método de acuerdo a la reivindicación 17 en la cual el trastorno del sueño consiste de narcolepsia y enuresis.

26. El método de acuerdo a la reivindicación 17 en la cual el trastorno somático consiste de trastornos de somatización, trastorno de conversión, trastorno de dolor, hipocondría, trastorno de dismorfia corpórea, trastorno no identificado somático y somatoformas NOS.

27. El método de acuerdo a la reivindicación 17 en el cual la incontinencia consta de una o más incontinencias debido al stress, incontinencia genuina de stress e incontinencia combinada.

28. El método de acuerdo a la reivindicación 17 en el cual dicha condición es de por lo menos un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, depresión, trastorno distímico, trastorno de ansiedad generalizada (GAD), adicción a la nicotina, trastorno de estrés post-traumático,

Eduardo Calado

trastorno disfórico premenstrual, trastorno sicótico, y (SSRI),
síndrome de defecarse.

29. El método de acuerdo a la reivindicación 28 en el cual dicha condición es por lo menos una de apatía, trastorno por déficit de atención debido a condiciones generales médicas, trastorno de déficit de atención por hiperactividad, síndrome de fatiga crónica, trastorno ciclotímico, depresión, adicción a la nicotina, trastorno de stress post-traumático, y (SSRI), síndrome de defecarse.

30. Un método para tratar un sufrimiento debido a una condición en el cual los inhibidores de norepinefrina proporcionan un beneficio, mientras que disminuye los efectos secundarios, el método consiste en suministrar una dosis total aproximada de 0.1 hasta alrededor de 10mg/día de una reboxetina, (S, S) ópticamente pura o una sal farmacéuticamente aceptable del mismo, a un individuo, y siendo dicha reboxetina (S, S) ópticamente pura y substancialmente libre de (R,R) reboxetina.

31. El método de acuerdo a la reivindicación 29 en la cual dichos efectos adversos consisten de mareos, insomnio, atolondramiento, cambios en presión sanguínea, sudores, trastornos intestinales,

disfunción sexual en hombres, efectos parecidos a anticolinérgicos, y efectos secundarios con interacción de drogas-drogas.

32. Un método para el tratamiento de trastornos del sistema nervioso, el cual consiste en los siguientes pasos: el suministro de una dosis terapéuticamente eficaz de reboxetina racémica o una sal farmacéuticamente aceptable del mismo a un individuo que necesite dicho tratamiento, en el cual dicho trastorno es por lo menos uno de los trastornos de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad, trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno de desarrollo específico, y (SSRI), síndrome de defecarse.

33. El método de acuerdo a la reivindicación 32 en el cual el trastorno es de por lo menos uno de los trastornos de acoplamiento, trastorno de déficit de aprendizaje debido a la edad, o trastorno mentao

Edwards Palacios

trastorno crónico o agudo debido al estrés, trastorno ciclotímico, trastorno distímico, trastorno de estrés post traumático, trastorno disfórico premenstrual, trastorno sicótico, y (SSRI) síndrome de defecarse .

34. El método de acuerdo a la reivindicación 33, en el cual dicho trastorno es por lo menos uno relacionado con la apatía, fatiga crónica, trastorno ciclotímico, trastorno de estrés post traumático y SSRI síndrome de defecarse.

35. El método de acuerdo a la reivindicación 32, en el cual la reboxetina se suministra al individuo en una cantidad aproximada de 2 hasta 20 mg/día.

36. El método de acuerdo a la reivindicación 33, en el cual la reboxetina se suministra en una cantidad aproximadamente de 4 hasta 10 mg/día.

37. El método de acuerdo a la reivindicación 36, en la cual la reboxetina se suministra aproximadamente de 6 hasta 10 mg/día.

Edwards Calado

252

38. El método de acuerdo a la reivindicación 32, en el cual dicha reboxetina se suministra por vía oral, parenteral, transdermica, rectal o vaginal.

39. El método de acuerdo a la reivindicación 38, en la cual dicha reboxetina se suministra oralmente con un portador farmacéuticamente aceptable, el cual consta de por lo menos un menos una substancia aglutinante, diluyente, lubricante, agente desintegrante, agente efervescente, materia colorante, dulcificante y agente húmedo.

40. El método de acuerdo a la reivindicación 39 en el cual el suministro oral es mediante un sachet, cápsula, tableta o aerosol.

41. El método de acuerdo a la Reivindicación 38 en la cual dicha reboxetina (S, S) se suministra parenteralmente subcutánea, intravenosa o intramuscular.

42. El método de acuerdo a la Reivindicación 32, en la cual la sal farmacéuticamente aceptable es metanosulfonado.

Eduardo Calado

traumático, trastorno disfórico premenstrual, trastorno sicótico,
trastorno temporal afectivo, trastorno de insomnio, trastorno de
desarrollo específico, y (SSRI), síndrome de defecarse.

Eduardo Calado

254

43. Una preparación de un medicamento de una composición que consta de reboxetina para tratar por lo menos un trastorno del sistema nervioso seleccionado del grupo que consiste de trastorno de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad y trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-traumático, trastorno disfórico premenstrual, trastorno sicótico, trastorno temporal afectivo, trastorno de insomnio, trastorno de desarrollo específico, y (SSRI), síndrome de defecarse.

44. El uso de la reboxetina para la fabricación de un medicamento para tratar por lo menos un trastorno del sistema nervioso seleccionado de un grupo que consiste de trastornos de acoplamiento, un trastorno de acoplamiento, trastorno de aprendizaje asociado con la edad y trastorno mental, anorexia nervosa, apatía, trastorno por déficit de atención debido a condiciones médicas generales, trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somáticos, obesidad, neuropatía periférica, trastorno de stress post-

Edwardo Calado

PA 258502



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 06, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/170,381

FILING DATE: December 13, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS



P. SWAIN

Certifying Officer



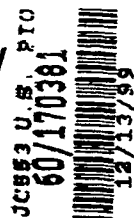
12-14-99

Approved 262

PROVISIONAL PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No: 28341/6248.3



256

PROVISIONAL PATENT APPLICATION TRANSMITTAL

**Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231**

Sir:

Transmitted herewith for filing is the provisional patent application under 37 CFR 1.53(c) of

Inventors:

- | | |
|---|---|
| 1. Erik H.F. Wong,
7352 Hampstead Lane
Portage, Michigan 49024 | 4. Robert McArthur
531 Carrington Court
Kalamazoo, Michigan 49009 |
| 2. Saeeduddin Ahmed
9889 Defoe Court
Portage, Michigan 49002 | 5. Duncan P. Taylor
8722 West F Avenue
Kalamazoo, Michigan 49009 |
| 3. Robert Clyde Marshall
7560 Fieldwood Circle
Mattawan, Michigan 49071 | 6. Lars Birgeron
54 Hillcrest Road
Martinsville, New Jersey 08836 |

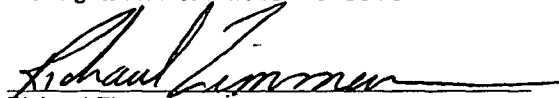
Title: **HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS AND METHODS OF USING THE SAME**

1. Application Papers Enclosed

- | | |
|----|--|
| 1 | Title Page |
| 26 | Pages of Specification (excluding Claims & Abstract) |
| 7 | Pages of Claims |
| 1 | Page of Abstract |

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Provisional Patent Application Transmittal and the documents referred to as enclosed therewith are being deposited with the United States Postal Service on **December 13, 1999**, in an envelope addressed to the Assistant Commissioner for Patents, Box Provisional Patent Application, Washington, D.C. 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing Label No. **EM099776733US**.


Richard Zimmermann

2. **Additional Papers Enclosed**

- ☐ Declaration of Biological Deposit
- ☐ Computer readable copy of sequence listing containing nucleotide and/or amino acid sequence
- ☐ Microfiche computer program
- ☐ Verified statement(s) claiming small entity status under 37 CFR 1.9 and 1.27
- ☐ Associate power of attorney
- ☐ Verified translation of a non-English patent application
- ☐ An assignment of the invention
- ☒ Return Receipt Postcard
- ☐ Other (e.g. declaration or oath)

3. **Filing Fee Calculation (37 CFR 1.16)**

- ☒ **Provisional Application (\$75.00/\$150.00)** Filing Fee: \$150.00
- ☐ **Other Fees (e.g. Recording Assignment)** Filing Fee: \$_____
- Total Fees Enclosed** \$150.00

4. **Method of Payment of Fees**

- ☒ Enclosed is our firm check in the amount of: \$150.00
- ☐ Charge Deposit Account No. 13-2855 in the amount of: \$_____
- A copy of this Transmittal is enclosed.
- ☐ Not enclosed

5. **Deposit Account and Refund Authorization**

The Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees which may be required during the pendency of this application under 37 CFR 1.16 or 37 CFR 1.17 or under other applicable rules (except payment of issue fees), to Deposit Account No. 13-2855. A copy of this Transmittal is enclosed.

Please refund any overpayment to Marshall, O'Toole, Gerstein, Murray & Borun at the address below.

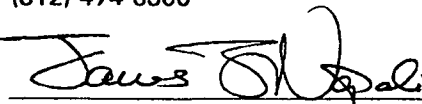
Please direct all future communications to James J. Napoli, at the address below.

258

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

By:


James J. Napoli
Reg. No: 32,361

December 13, 1999

60606-6402

JOINT INVENTORS

Attorney Docket No. 28341/6248.3

259

"EXPRESS MAIL" mailing label No. EM099776733US.

Date of Deposit: December 13, 1999

I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Box Provisional Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20281


Richard Zimmermann

PROVISIONAL APPLICATION FOR
UNITED STATES LETTERS PATENT

S P E C I F I C A T I O N

TO ALL WHOM IT MAY CONCERN:

Be it known that we, Erik H.F. Wong, a citizen of the United States of America, residing at 7352 Hampstead Lane, Portage, Michigan 49024, Kalamazoo County; Saeeduddin Ahmed, a citizen of the United States of America, residing at 9889 Defoe Court, Portage, Michigan, 49002, Kalamazoo County; Robert Clyde Marshall, a citizen of the United Kingdom, residing at 7560 Fieldwood Circle, Mattawan, Michigan, 49071, Van Buren County; Robert McArthur, a citizen of the United Kingdom and Canada, residing at 531 Carrington Court, Kalamazoo, Michigan, 49009, Kalamazoo County; Duncan P. Taylor, a citizen of the United States of America, residing at 8722 West F Avenue, Kalamazoo, Michigan, 49009, Kalamazoo County; and Lars Birgersson, 54 Hillcrest Road, Martinsville, New Jersey, 08836, have invented new and useful "HIGHLY SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS AND METHODS OF USING THE SAME," of which the following is a specification.

Attorneys for Applicants:

James J. Napoli (Reg. No. 32,361)
Marshall, O'Toole, Gerstein,
Murray & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402

NEW TREATMENTS FOR SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods of treating individuals suffering from a variety of conditions wherein inhibiting reuptake of
5 norepinephrine provides a benefit. In particular, the present invention relates to methods of treatment comprising administration of reboxetine to an individual to selectively inhibit the reuptake of norepinephrine.

Brief Description of Related Technology

Many types of depression, mental, behavioral, and neurological
10 disorders originate from disturbances in brain circuits that convey signals using certain monoamine neurotransmitters. Monoamine neurotransmitters include, for example, norepinephrine (noradrenaline), serotonin (5-HT), and dopamine. Lower-than-normal levels of norepinephrine are associated with a variety of symptoms including lack of energy, motivation, and interest in life. Thus, a
15 normal level of norepinephrine is essential to maintaining drive and capacity for reward.

These neurotransmitters travel from the terminal of a neuron across a small gap (*i.e.*, the synaptic cleft) and bind to receptor molecules on

the surface of a second neuron. This binding elicits intracellular changes that initiate or activate a response or change in the postsynaptic neuron.

Inactivation occurs primarily by transport (*i.e.*, reuptake) of the neurotransmitter back into the presynaptic neuron. Abnormality in noradrenergic transmission results in various types of depression, mental, behavioral, and neurological disorders attributed to a variety of symptoms including a lack of energy, motivation, and interest in life. *See generally*, R.J. Baldessarini, "Drugs and the Treatment of Psychiatric Disorders: Dépression and Mania" in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, NY, NY, pp. 432-439 (1996).

Reboxetine (*i.e.*, 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine) raises the concentration of physiologically active norepinephrine by preventing reuptake of norepinephrine, for example. Reboxetine is a norepinephrine reuptake inhibitor and has been shown to be effective in the short-term (*i.e.*, less than eight weeks) and long-term treatment of depression. In fact, reboxetine has been shown to have effectiveness that is similar to fluoxetine, imipramine, and desipramine, commonly prescribed antidepressants, in both adults and elderly patients. *See* S.A. Montgomery, *Reboxetine: Additional Benefits to the Depressed Patient*, *Psychopharmacol (Oxf)* 11:4 Suppl., S9-15 (Abstract) (1997).

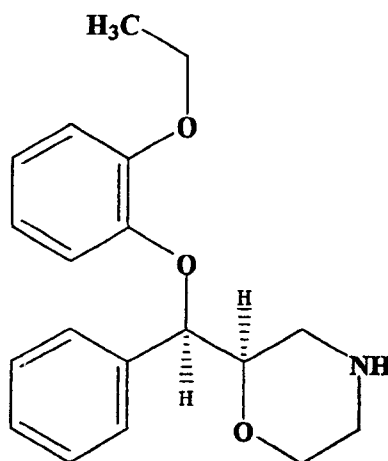
Antidepressant drugs are sometimes divided into "generations." The first generation included the monoamine oxidase inhibitors (such as isocarboxazid and phenylhydrazine) and tricyclic agents (such as imipramine). The second generation of antidepressant drugs included compounds such as mianserin and trazodone. The third generation has included drugs called selective reuptake inhibitors (*e.g.*, fluoxetine, sertraline, paroxetine, and reboxetine). Those drugs were characterized by relatively selective action on only one of the three main monoamine systems thought to be involved in depression (*i.e.*, 5-HT (serotonin), noradrenaline (norepinephrine), and dopamine). *APP Textbook of Psychopharmacology* (A.F. Schatzberg and C.B.

268
262

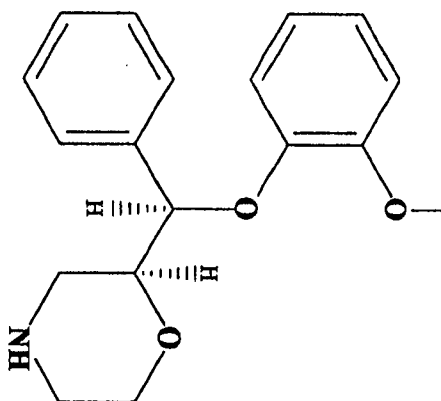
Nemeroff), American Psychiatric Press, 2d. ed., (1998); Lexicon of Psychiatry, Nuerology and the Neurosciences (F.J. Ayd, Jr.) Williams and Wilkins (1995). The antidepressant efficacy of reboxetine is evidenced by its ability to prevent reserpine-induced blepharospasm and hypothermia in mice, down regulation of β -adrenergic receptors and desensitization of noradrenaline-coupled adenylate cyclase. See M. Brunello and G. Racagni, "Rationale for the Development of Noradrenaline Reuptake Inhibitors," Human Psychopharmacology, vol. 13, S-13-519, Supp. 13-519 (1998).

Reboxetine generally is described in Melloni *et al.* U.S. Patent Nos. 4,229,449, 5,068,433, and 5,391,735, and in GB 2,167,407, the disclosures of which are hereby incorporated by reference. Chemically, reboxetine has two chiral centers and, therefore, exists as two enantiomeric pairs of diastereomers, shown below as isomers (I) through (IV):

(I)



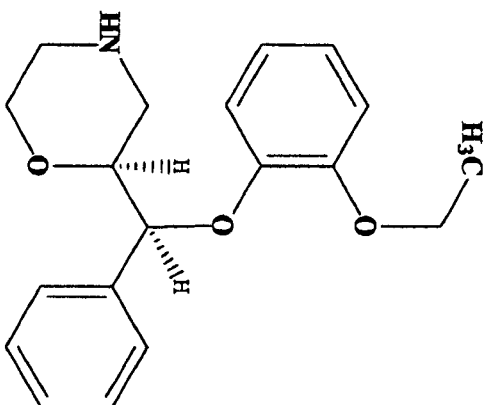
(R, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine



(R, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

263a

(II) 263



5

10

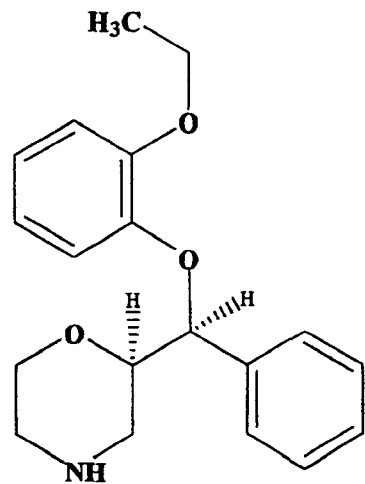
(S, S) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

(III)



(IV)

5



(S, R) 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine

10

15

20

Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes D and L, or (+) or (-), designate the sign of rotation of plane-polarized light by the compound, with L or (-) meaning that the compound is levorotatory. In contrast, a compound prefixed with D or (+) is dextrorotatory. There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. Thus, D-lactic acid is the same as (-)-lactic acid, and L-lactic acid is the same as (+)-lactic acid. For a given chemical structure, each of a pair of enantiomers are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric, or racemic, mixture.

25

Stereochemical purity is important in the pharmaceutical field, where many of the most often prescribed drugs exhibit chirality. For example, the L-enantiomer of the beta-adrenergic blocking agent, propranolol, is known

to be 100 times more potent than its D-enantiomer. Additionally, optical purity is important in the pharmaceutical drug field because certain isomers have been found to impart a deleterious effect, rather than an advantageous or inert effect. For example, it is believed that the D-enantiomer of thalidomide is a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, whereas its corresponding L-enantiomer is believed to be a potent teratogen.

When two chiral centers exist in one molecule, there are four possible stereoisomers: (R,R), (S,S), (R,S), and (S,R). Of these, (R,R) and (S,S) are an example of a pair of enantiomers (mirror images of each other), which typically share chemical properties and melting points just like any other enantiomeric pair. The mirror images of (R,R) and (S,S) are not, however, superimposable on (R,S) and (S,R). This relationship is called diastereoisomeric, and the (S,S) molecule is a diastereoisomer of the (R,S) molecule, whereas the (R,R) molecule is a diastereoisomer of the (S,R) molecule.

Currently, reboxetine is commercially available only as a racemic mixture of enantiomers, (R,R) and (S,S) in a 1:1 ratio, and reference herein to the generic name "reboxetine" refers to this enantiomeric, or racemic, mixture. Reboxetine is commercially sold under the trade names of EDRONAX™, PROLIFT™, VESTRA™, and NOREBOX™. As previously noted, reboxetine has been shown to be useful in the treatment of human depression. Orally administered reboxetine is readily absorbed and requires once or twice a day administration. A preferred adult daily dose is in the range of about 8 to about 10 milligrams (mg). The effective daily dosage of reboxetine for a child is smaller, typically in a range of about 4 to about 5 mg. The optimum daily dosage for each patient, however, must be determined by a treating physician taking into account the patient's size, other medications which the patient may be taking, identity and severity of the particular disorder, and all of the other circumstances of the patient.

272
266

Administration of reboxetine, however, can result in undesired side effects associated with drug-drug interactions and in other undesirable effects such as, for example, dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in males, certain anticholinergic-like effects (*e.g.*, tachyarrhythmia and urinary retention).

Accordingly, there is a need in the art for a method of treating individuals suffering from a variety of conditions where inhibiting reuptake of norepinephrine provides a benefit, while reducing or eliminating the adverse side effects associated with conventional norepinephrine reuptake inhibitors. There also is a need for a method that selectively inhibits the reuptake of norepinephrine over other neurotransmitters, like serotonin and dopamine.

SUMMARY OF THE INVENTION

The present invention generally is directed to methods of treating or preventing a variety of conditions where inhibition of norepinephrine reuptake provides a benefit. More particularly, the present invention is directed to an effective treatment or prevention of such conditions comprising administration of reboxetine, or an optically pure (S,S) stereoisomer thereof, to a human. Individuals treated with optically pure (S,S) reboxetine do not experience certain adverse side effects associated with the administration of the racemic mixture of (R,R) and (S,S) reboxetine. The present invention therefore includes administering optically pure (S,S) reboxetine to a human to selectively inhibit norepinephrine reuptake, and thereby control, reduce, or eliminate adverse effects caused by the administration of the racemic mixture of reboxetine.

More specifically, one embodiment of the present invention is directed to a method of treating or preventing a human condition wherein inhibiting reuptake of norepinephrine provides a benefit. The method

267

267

comprises the step of administering a therapeutic amount, typically about 0.5 to about 10 mg/day, of optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. Optically pure (S,S) reboxetine is substantially free of (R,R) reboxetine.

5 Human conditions that can be treated and/or prevented by
inhibiting the reuptake of norepinephrine include, but are not limited to,
addictive disorders (including those due to alcohol, nicotine, and other
psychoactive substances) and withdrawal syndrome, adjustment disorders
10 (including depressed mood, anxiety, mixed anxiety and depressed mood,
disturbance of conduct, and mixed disturbance of conduct and mood), age-
associated learning and mental disorders (including Alzheimer's disease),
anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to
general medical conditions, attention-deficit hyperactivity disorder (ADHD),
bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute
15 stress, conduct disorder, cyclothymic disorder, depression (including
adolescent depression and minor depression), dysthymic disorder, fibromyalgia
and other somatoform disorders (including somatization disorder, conversion
disorder, pain disorder, hypochondriasis, body dysmorphic disorder,
undifferentiated somatoform disorder, and somatoform NOS), generalized
20 anxiety disorder (GAD), incontinence (*i.e.*, stress incontinence, genuine stress
incontinence, and mixed incontinence), inhalation disorders, intoxication
disorders (alcohol addiction), migraine headaches, obesity (*i.e.*, reducing the
weight of obese or overweight patients), obsessive compulsive disorders and
related spectrum disorders, oppositional defiant disorder, panic disorder,
25 peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric
disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder),
psychotic disorders (including schizophrenia, schizoaffective and
schizophreniform disorders), seasonal affective disorder, sleep disorders (such
as narcolepsy and enuresis), social phobia (including social anxiety disorder),
30 specific developmental disorders, and selective serotonin reuptake inhibition
(SSRI) "poop out" syndrome (*i.e.*, wherein a patient who fails to maintain a

27A
268

satisfactory response to SSRI therapy after an initial period of satisfactory response).

Optically pure (S,S) reboxetine is advantageous over prior treatment or prevention methods which utilized a racemic mixture of (R,R) and (S,S) reboxetine. In particular, it has been found that treatments using compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Therefore, reuptake blockage can be achieved with much lower dosages. Accordingly, the present invention may permit a substantial reduction in the customary daily dosage of the racemic mixture (*i.e.*, the commercially available reboxetine) by about 50% to about 80% because of the use of an optically pure (S,S) reboxetine. In addition, treatments utilizing the optically pure (S,S) reboxetine may result in fewer undesirable adverse side effects associated with the treatment because of the high selectivity and potency of (S,S) reboxetine with respect to inhibiting the reuptake of norepinephrine.

Another embodiment of the present invention is directed to a method of treating or preventing a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine to an individual, wherein the disorder is at least one of adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), migraine headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients),

peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome. Other embodiments of the present invention are directed to a preparation of a medicament from a composition comprising reboxetine and a use of reboxetine in a manufacture of the medicament to treat or prevent at least one of the aforementioned nervous system disorders.

Additional benefits and features of the present invention will become apparent to those skilled in the art from a review of the following detailed description, taken in conjunction with the example and the appended claims. It should be noted, however, that while the invention is susceptible of embodiments in various forms, described hereafter are specific preferred embodiments of the invention with the understanding that the present disclosure is intended as illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reboxetine is a known compound that is active on the central nervous system. Reboxetine has been used as an antidepressant, and has been suggested for the treatment of oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder. These proposed treatments are disclosed in International Publication Nos. WO 99/15163, WO 95/15176, and WO 99/15177.

Heretofore, use of reboxetine has been limited to the treatment of depression, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder. Furthermore, prior treatment methods using

276
270

reboxetine administered a racemic mixture of the (S,S) and (R,R) stereoisomers. One embodiment of the present invention, however, is directed to an effective method using an optically pure (S,S) stereoisomer of reboxetine to treat or prevent conditions wherein inhibition of reuptake of norepinephrine is beneficial. (S,S) Reboxetine is an effective, selective inhibitor of norepinephrine reuptake and, accordingly, dose levels can be substantially reduced in comparison to racemic reboxetine. In addition, individuals treated with an optically pure (S,S) reboxetine do not experience certain adverse effects associated with the administration of the racemic mixture of (R,R) and (S,S) reboxetine. Accordingly, one embodiment of the present invention includes administering a therapeutic amount of an optically pure (S,S) reboxetine to a human to inhibit the reuptake of norepinephrine, and to control, reduce, or eliminate adverse effects associated with administration of racemic reboxetine.

More specifically, one embodiment of the present invention is directed to a method of treating or preventing a human condition wherein inhibiting reuptake of norepinephrine provides a benefit. The method comprises the step of administering, and preferably orally administering, a total dose of about 0.5 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual. The optically pure (S,S) reboxetine is substantially free of (R,R) reboxetine.

As used herein, the term "reboxetine" refers to the racemic mixture of the (R,R) and (S,S) enantiomers of reboxetine. In contrast, the term "(S,S) reboxetine" refers to only the (S,S) stereoisomer. Similarly, the term "(R,R) reboxetine" refers to only the (R,R) stereoisomer.

The phrases "optically pure (S,S) reboxetine" and "substantially free of its (R,R) stereoisomer," as used herein, mean that the composition contains a greater proportion of (S,S) reboxetine in relation to (R,R) reboxetine. In a preferred embodiment, the phrases mean that the composition is at least 90 percent by weight (wt.%) of (S,S) reboxetine, and 10 wt.% or less

271

of (R,R) reboxetine. In a more preferred embodiment the phrases mean that the composition contains at least 97 wt.% of (S,S) reboxetine, and 3 wt.% or less of (R,R) reboxetine. In an even more preferred embodiment, the phrases mean that the composition contains at least 99 wt.% of (S,S) reboxetine, and 1 wt.% or less of (R,R) reboxetine. In a most preferred embodiment, the phrases "optically pure (S,S) reboxetine" and "substantially free of its (R,R) stereoisomer," as used herein, mean that the composition contains greater than 99 wt.% of (S,S) reboxetine. The foregoing percentages are based upon the total amount of reboxetine present in the composition. The phrases "substantially free of (R,R) reboxetine," "substantially optically pure (S,S) stereoisomer of reboxetine," "substantially optically pure (S,S) reboxetine," "optically pure (S,S) stereoisomer of reboxetine," and "optically pure (S,S) reboxetine" are also encompassed by the above-described amounts.

The phrases "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases. Because the active compound (*i.e.*, (S,S) reboxetine) used in the present invention is basic, salts may be prepared from pharmaceutically acceptable acids. Suitable pharmaceutically acceptable acids include acetic, benzenesulfonic (besylate), benzoic, p-bromophenylsulfonic, camphorsulfonic, carbonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, isethionic, lactic, maleic, malic, mandelic, methanesulfonic (mesylate), mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like.

Examples of such pharmaceutically acceptable salts of (S,S) reboxetine, thus, include, but are not limited to, acetate, benzoate, β -hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate,

naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, and the like. A preferred pharmaceutical salt of (S,S) reboxetine is methanesulfonate (*i.e.*, mesylate), which is prepared using methanesulfonic acid.

The phrases "adverse effects" and "adverse side effects" in relation to reboxetine include, but are not limited to, dizziness, insomnia, lightheadedness, changes in blood pressure, gastrointestinal disturbances, sexual dysfunction in males, extrapyramidal side effects, certain anticholinergic-like effects (*e.g.*, tachycardia, blurred vision), and undesired side effects associated with drug-drug interactions.

More specifically, administration of an optically pure (S,S) reboxetine is effective in treating and/or preventing various human conditions including, but not limited to, addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances) and withdrawal syndrome, adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression (including adolescent depression and minor depression), dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder (GAD), incontinence (*i.e.*, stress incontinence, genuine stress incontinence, and mixed incontinence), inhalation disorders, intoxication disorders (alcohol addiction), migraine

279
273

headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients),
obsessive compulsive disorders and related spectrum disorders, oppositional
defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress
disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late
5 luteal phase dysphoric disorder), psychotic disorders (including schizophrenia,
schizoaffective and schizophreniform disorders), seasonal affective disorder,
sleep disorders (such as narcolepsy and enuresis), social phobia (including
social anxiety disorder), specific developmental disorders, and selective
serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a
10 patient who fails to maintain a satisfactory response to SSRI therapy after an
initial satisfactory response). Reference to treatments for "nicotine addiction"
herein also includes treatments for smoking cessation. Many of the foregoing
human conditions are generally described by the American Psychiatric
Association in their publication entitled, "Diagnostic and Statistical Manual of
15 Mental Disorders," 4th ed. rev. (Washington D.C. 1994), the disclosure of
which is hereby incorporated by reference. General descriptions of addictive
disorders, including disorders related to intoxication and inhalants and, and
nicotine addiction may be found in many standard references, such as R.E.
Hales *et al.*, "The American Psychiatric Press Textbook of Psychiatry," 3d. ed.
20 (1999), the disclosure of which is hereby incorporated by reference.

As noted above, (S,S) reboxetine also can be used to prevent or
treat migraine headaches. Furthermore, (S,S) reboxetine can be used to treat
or prevent headaches in migraineurs or people suffering from migraine
headaches, including the treatment of symptoms of an existing headache,
25 treatment to prevent the occurrence, intensity, and duration of a headache,
prophylactic use to prevent or reduce the incidence or duration of migraines, as
an adjuvant to facilitate the effectiveness of an abortive medication or co-
administered with other medications (including abortive medications) to reduce
the required dosages (and side effects) of those medications.

As used herein, the terms "treat," "treatment," and "treating," extend to prophylaxis, in other words "prevent," "prevention," and "preventing," as well as treatment of established conditions. Accordingly, use of the terms "prevent," "prevention," and "preventing," would be an administration of the pharmaceutical composition to a person who has in the past suffered from the aforementioned conditions, such as, for example, migraine headaches, but is not suffering from the conditions at the moment of the composition's administration.

The administration of (S,S) reboxetine is very effective in the treatment and/or prevention of addictive disorders and withdrawal syndromes, adjustment disorders, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine addiction, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, schizoaffective disorder, and SSRI "poop out" syndrome. Furthermore, the administration of (S,S) reboxetine is especially effective in treatment or prevention of addictive disorders and withdrawal syndromes, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, chronic fatigue syndrome, chronic or acute stress, dysthymic disorder, depression, nicotine addiction, obesity, post-traumatic stress disorder, and SSRI "poop out" syndrome.

It is known that commercially-available reboxetine is a racemic mixture of the (R,R) and (S,S) enantiomers of 2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine. It has now been discovered that the (S,S) stereoisomer is the most active and the most selective stereoisomer with respect to inhibiting the reuptake of norepinephrine. In addition, when administered to an individual, in the dosages described herein, as an optically pure material (*i.e.*, in the substantial absence of its (R,R) diastereomer), the individual does not experience many of the adverse side effects associated with

the administration of commercially-available reboxetine. Furthermore, it has further been discovered that the (S,S) and (R,R) enantiomers have a reversed selectivity for the norepinephrine neurotransmitter in relation to the serotonin neurotransmitter, and an optically pure (S,S) reboxetine is significantly more effective at inhibiting reuptake of norepinephrine than either the (R,R) enantiomer or a racemic mixture of the (S,S) and (R,R) enantiomers.

Specifically, it has been found that compositions containing an optically pure (S,S) reboxetine are about 5 to about 8.5 times more effective at inhibiting the reuptake of norepinephrine than compositions containing the racemic mixture of the (R,R) and (S,S) stereoisomers. Accordingly, the typical daily dosage of the racemic mixture (*i.e.*, commercially available reboxetine) can be reduced by about 50% to about 80% when using an optically pure (S,S) reboxetine. The reduction in dosage does not lead to a reduction in efficacy, but the reduction or elimination of various adverse side effects was observed.

In particular, because an optically pure (S,S) reboxetine selectively inhibits norepinephrine reuptake compared to serotonin reuptake, adverse side effects associated with serotonin reuptake are reduced or eliminated. Such adverse side effects include, but are not limited to, gastrointestinal disturbances, anxiety, sexual dysfunction, and undesirable side effects associated with drug-drug interactions.

The synthesis of a racemic mixture of reboxetine is disclosed in Melloni *et al.* U.S. Patent No. 4,229,449. Individual stereoisomers of reboxetine can be obtained by resolution of the racemic mixture of enantiomers using conventional methods generally known by those skilled in the art. Such methods include, but are not limited to, resolution by simple crystallization and chromatographic techniques, for example, as set forth in GB 2,167,407.

The compounds of this invention may be administered in oral unit dosage forms such as tablets, capsules, pills, powders, or granules. They may also be introduced parenterally, (*e.g.*, subcutaneously, intravenously, or

intramuscularly), using forms known in the pharmaceutical art. They also may be administered rectally or vaginally in such forms as suppositories or bougies. These compounds also may be administered transdermally, such as with a "patch" containing active ingredient. In general, the preferred route of administration is oral, with a once or twice a day administration. The dosage regimen and amount for treating patients with the compounds of this invention is selected in accordance with a variety of factors including, for example, the type, age, weight, sex, and medical condition of the patient, the severity of the condition, the route of administration and the particular compound employed, either racemate or pure enantiomer. An ordinarily skilled physician or psychiatrist can readily determine and prescribe an effective amount of the compound to prevent or arrest the progress of the condition. In so proceeding, the physician or psychiatrist could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained. In general, reboxetine has a good safety profile and requires minimal titration.

Pharmaceutical compositions suitable for oral reboxetine administration can be of any convenient form, such as sachets, tablets, capsules, pills, or aerosol sprays, each containing a predetermined amount of the active compound either as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions can be prepared by any method that includes the step of bringing the active compound either into intimate association with a carrier, which constitutes one or more necessary or desirable ingredients. Generally, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into a desired form.

For example, a tablet can be prepared by compression or molding techniques, optionally, using one or more accessory ingredients. Compressed tablets can be prepared by compressing the active ingredient in a

suitable machine into a free-flowing form, such as a powder or granules. Thereafter, the compressed, free-flowing form optionally can be mixed with a binders, diluents, lubricants, disintegrating agents, effervescing agents, dyestuffs, sweeteners, wetting agents, and non-toxic and pharmacologically inactive substances typically present in pharmaceutical compositions. Molded tablets can be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine.

Suitable binders for use in the pharmaceutical preparation include, for example, starches, gelatine, methylcellulose, gum arabic, tragacanth, and polyvinylpyrrolidone. Suitable diluents for use in the pharmaceutical preparation include, for example, lactose, dextrose, sucrose, mannitol, sorbitol, and cellulose. Suitable lubricants for use in the pharmaceutical preparation include, for example, silica, talc, stearic acid, magnesium or calcium stearate, and or polyethylene glycols. Suitable disintegrating agents for use in the pharmaceutical preparation include, for example, starches, alginic acid, and alginates. Suitable wetting agents for use in the pharmaceutical preparation include, for example, lecithin, polysorbates, and laurylsulfates. Generally, any effervescing agents, dyestuffs, and/or sweeteners known by those of ordinary skill in the art can be used in the preparation of a pharmaceutical composition.

Desirably, daily dose of the composition (e.g. tablet, sachet, or capsule) contains from about 0.1 to about 10 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably, each dose of the composite contains about 0.5 to about 8 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. Even more preferably, however, each dose contains from about 0.5 to about 5 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 2.5 mg to be administered in one or two oral doses. This will allow for tablets containing 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7,

0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5 mg of optically pure (S,S) reboxetine.

5 In another embodiment, a preferred daily dose of the composition (e.g., tablet, sachet, or capsule) contains from about 0.1 to about 0.9 mg of optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. More preferably, each dose of the composition contains about 0.5 to about 0.8 mg of the active ingredient, optically-pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. Even more preferably, however, each dose contains from about 0.5 to about 0.75 mg of the active
10 ingredient, optically pure (S,S) reboxetine, and is substantially free of its (R,R) stereoisomer. This dosage form permits the full daily dosage of about 0.5 to about 0.9 mg to be administered in one oral dose.

15 Patients suffering from depression, nicotine addiction, conduct disorder, oppositional defiant disorder, and/or attention-deficit hyperactivity disorder will benefit from the administration of optically pure (S,S) reboxetine regardless of these or other co-morbid conditions. Diagnostic criteria for these disorders generally are provided by the American Psychiatric Association and published in their "Diagnostic and Statistical Manual of Mental Disorders," 4th ed. rev. (Washington D.C. 1994), and in International Publication Nos. WO
20 99/15177, WO 99/15176, and WO 99/15163, the disclosures of which are hereby incorporated by reference.

25 Furthermore, patients suffering from addictive disorders and withdrawal syndromes, adjustment disorders, apathy, attention-deficit hyperactivity disorder, attention-deficit disorders due to medical conditions, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, depression, dysthymic disorder, generalized anxiety disorder (GAD), nicotine addiction, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, schizoaffective disorder, and SSRI "poop out" syndrome will benefit from the administration of optically pure (S,S) reboxetine.

These disorders display similar patterns in children, adolescents, and adults. Hence, methods of the present invention are effective in the treatment of child, adolescent, and adult patients. For purposes of the present invention, a child is considered to be a person below the age of puberty, an
5 adolescent is considered to be a person between the age of puberty and up to about 18 years of age, and an adult generally is a person of at least about 18 years of age. As previously noted, the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's size, other medications which the patient is taking, identity and severity of the
10 disorder, and all of the other circumstances of the patient.

As stated above, reboxetine acts as an antidepressant. Reboxetine, however, does not act like most antidepressants. Unlike tricyclic antidepressants, and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that
15 reboxetine is not a selective serotonin reuptake inhibitor. Rather, reboxetine is selective for the noradrenergic system. Reboxetine is not an SSRI, but is a novel, selective, noradrenaline reuptake inhibitor (NRI). B. Leonard, "Noradrenaline in basic models of depression." *European-Neuropsychopharmacol*, 7 Suppl. 1 pp. S11-6 and S71-3 (Apr., 1997). Unlike
20 most prior generation drugs, reboxetine is a highly selective norepinephrine reuptake inhibitor, with only marginal serotonin and no dopamine reuptake inhibitory activity. Reboxetine displays no anticholinergic binding activity in different animal models, and is devoid of monoamine oxidase (MAO) inhibitory activity.

Reboxetine also is a highly potent, pharmacologically specific, and fast acting agent. Investigations indicate that reboxetine has potent antireserpine activity, and combines the inhibitory properties of classical
25 tricyclic antidepressants on the reuptake of noradrenaline with an ability to desensitize β -adrenergic receptor function, without showing any appreciable
30 blocking action at muscarinic, cholinergic, histaminergic, and α -adrenergic

receptors. Moreover, reboxetine shows less vagolytic activity than tricyclic antidepressants, and no evidence of cardiotoxicity.

5 Accordingly, in another embodiment of the invention, racemic reboxetine can be used to treat or prevent a number of mental and neurological disorders. Specifically, reboxetine has been found particularly useful for
10 treating or enhancing the treatment or prevention of a variety of psychiatric symptoms or disorders, with greater efficacy and with fewer side effects than with treatment by known drugs. Furthermore, reboxetine may also be used to treat, or to enhance the treatment or prevention of, other specific psychiatric symptoms or disorders.

15 Mental and neurological disorders that may be treated or prevented by administration of a therapeutically effective amount of a racemic reboxetine (or a derivative or pharmaceutically acceptable salts thereof) include, but are not limited to adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed
20 disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform
25 disorder, and somatoform NOS), incontinence (*i.e.*, stress incontinence, genuine stress incontinence, and mixed incontinence), migraine headaches, obesity (*i.e.*, reducing the weight of obese or overweight patients), peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such

as narcolepsy and enuresis), specific developmental disorders, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

Similar to (S,S) reboxetine, racemic reboxetine also can be used to treat humans suffering from migraine headaches, particularly to reduce the frequency, duration, intensity, and or complications resulting from migraine headaches. Furthermore, racemic reboxetine can be used to prevent migraine headaches.

Additionally, racemic reboxetine can be used to treat incontinence (*i.e.*, stress incontinence, genuine stress incontinence, and mixed incontinence). Stress urinary incontinence is a symptom describing involuntary loss of urine on carrying out any activity that raises intra-abdominal pressure such as coughing or sneezing. Stress incontinence is also a clinical sign, that is the observation by a care giver of a jet of urine escaping from the urethral meatus (opening) when the patient coughs or strains. Genuine Stress Incontinence is the pathological diagnosis of an incompetent urethral sphincter as diagnosed by Urodynamic testing. Mixed incontinence is stress incontinence in combination with urge incontinence. The latter is a part of the symptom complex of the Overactive Bladder. Retention may be due to outflow obstruction (*e.g.*, high urethral pressure), poor detrusor (bladder muscle) contractility or lack of coordination between detrusor contraction and urethral relaxation.

The racemate form of reboxetine is well tolerated and has a wide safety range. Racemic reboxetine can be administered to an individual in an amount in a range of about 2 to about 20 milligrams per patient per day (mg/day), and preferably about 4 to about 10 mg/day, and more preferably about 6 to about 10 mg/day. Depending upon the formulation and the individual's disorder, the total daily dosage can be administered in small amounts up to two times a day. Reboxetine typically is administered orally, for example, in the form of tablets, but can be administered parentally, transdermally, rectally, or vaginally.

A preferred method of administering racemic reboxetine is oral dosing once or twice a day. It can also be administered at dosages of about 2, 4, 6, 8, 10, or 12 mg/day or fractions thereof. For example, suitable administrations could be about 4 mg in the morning and about 2 or about 4 mg in the afternoon or evening. In some patients, the ideal dosing would be about 3 to about 5 mg in the morning and about 3 to about 5 mg in the afternoon. A skilled physician or psychiatrist can determine the precise level of dosing. The ideal dosing is routinely determined by an evaluation of clinical trials and the needs of specific patients.

In accordance with the present invention, the racemic reboxetine also can be administered as the free base or a pharmaceutically acceptable salt thereof. The phrases "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases as described above with respect to the salts of optically pure (S,S) reboxetine. A preferred pharmaceutical salt of reboxetine is methanesulfonate (*i.e.*, mesylate), which is prepared using methanesulfonic acid.

Treatment or prevention of above disorders involves the administration of reboxetine in a manner and form that result in a reduction in the symptoms of the disease or disorder. Typically, the symptoms exhibited by children, adolescents, and adults are similar to each other. Hence, methods of the present invention are effective in the treatment of child, adolescent, and adult patients.

EXAMPLE

This example demonstrates the superior selectivity of (S,S) reboxetine compared to its (R,R) stereoisomer and to racemic reboxetine.

Sprague-Dawley rats weighing about 250 to about 300 grams were decapitated, and cerebral cortical tissue was removed immediately. Cerebral cortices were homogenized in nine volumes of medium each containing 0.32 M sucrose using a rotating pestle. The obtained homogenate was centrifuged at about 1000 x g for about 10 minutes at about 4°C. A supernatant was collected and further centrifuged at about 20,000 x g for about 20 minutes at a temperature of about 4°C. A protein pellet resulting from the centrifuge steps was re-suspended in a Kreb's-Hepes buffer to result in a protein concentration of about 2 mg/ml of buffer. The buffer was maintained at a pH of about 7.0 and contained: 20 mM Hepes; 4.16 mM NaHCO₃; 0.44 mM KH₂PO₄; 0.63 mM NaH₂PO₄; 127 mM NaCl; 5.36 mM KCl; 1.26 mM CaCl₂; and 0.98 mM MgCl₂.

Protein/buffer suspension was introduced into 165 assay tubes such that about 30 µg (10⁻⁶ grams) to about 150 µg of the protein was added to each of 166 assay tubes (*i.e.*, 80 assays per transporter assay). Synaptosomal uptake of ³H-norpinephrine was determined as follows. About 1.4 nanomolar of [³H]citalopram and about 1.9 nM of [³H]nisoxetine were used to label serotonin and norepinephrine reuptake sites, respectively. Nonspecific binding was defined by 100 micromolar (µM) fluoxetine (for serotonin) and 10 µM desipramine (for norepinephrine). Incubation in total assay volume of about 500 microliters (µl) was carried out for about 60 minutes (for serotonin) and 120 minutes (for norepinephrine). Both incubations were carried out at about 25°C, and terminated by rapid filtration through a 48-well cell harvester through GFB filters (pre-soaked with about 0.5 PEI for about 4 hours) in a 3 x 5 ml of ice-cold 200 mM tris-HCl, pH 7.0. Punched-out filters were placed into 7 ml minivials and radioactive assayed by liquid scintillation counting.

The ability of reboxetine (*i.e.*, racemic mixture of (R,R) and (S,S) reboxetine), (R,R) reboxetine, and (S,S) reboxetine to bind to norepinephrine and serotonin reuptake sites was evaluated in binding assays using the two radioligands, [³H]citalopram and [³H]nisoxetine. The

concentration of the test compound required to inhibit 50% of the ³H-norpinephrine accumulation and ³H-serotonin (IC₅₀ values) were determined by linear regression analysis. A conversion of IC₅₀ values to Ki values was carried out using the Cheng-Prassoff equation presented below:

5
$$K_i = IC_{50} / (1 + ([L] / [K_d \text{ of } L]))$$

wherein [L] is the radioligand concentration used in nM, and K_d is the binding affinity of L in nM.

The Ki values calculated according to the Cheng-Prassoff equation are provided in the table below:

10

Table			
Compound	Norepinephrine Reuptake (Ki nM)	Serotonin Reuptake (Ki nM)	Selectivity of Ki of Serotonin/Norepinephrine
(S,S) Reboxetine	0.23 ± 0.06	2937 ± 246	12,770
(R,R) Reboxetine	7.0 ± 1.7	104 ± 43	15
Reboxetine	1.6 ± 0.6	129 ± 13	81

15

The data shows that (S,S) reboxetine is about five to about eight fold more potent than the reboxetine racemate with respect to inhibiting the reuptake of norepinephrine. In addition, racemic reboxetine has an 81 fold selectivity favoring norepinephrine reuptake inhibition over serotonin reuptake inhibition. Unexpectedly, the enantiomeric selectivity of the (S,S) and (R,R) reboxetine stereoisomers with respect to inhibiting the reuptake of norepinephrine and serotonin are quite different. The (S,S) enantiomer is very poor with respect to inhibiting reuptake of serotonin (*i.e.*, a high Ki) and, therefore, has a surprisingly high selectivity for the norepinephrine reuptake site. In particular, the selectivity of serotonin versus norepinephrine increases from 81 (for the racemate) to 12,770 for an optically pure (S,S) reboxetine. Accordingly, administration of a therapeutic dose of (S,S) reboxetine effectively inhibits norepinephrine reuptake, but serotonin reuptake essentially

20

25

is not affected. As a consequence, adverse side effects associated with the inhibition of serotonin reuptake are not manifested.

Surprisingly, this effect is not observed with (R,R) reboxetine, but are quite to the contrary. (R,R) reboxetine is a weaker inhibitor than (S,S) reboxetine with respect to norepinephrine reuptake, *i.e.*, affinity (*i.e.*, K_i) for (R,R) reboxetine is 7 nM whereas the K_i for (S,S) reboxetine is 0.23 nM. In addition, (R,R) reboxetine is much more effective at inhibiting serotonin uptake than (S,S) reboxetine, *i.e.*, K_i for (R,R) reboxetine is 104 nM, whereas the K_i for (S,S) reboxetine is 2937 nM. Accordingly, (R,R) reboxetine has a low selectivity for norepinephrine reuptake inhibition versus serotonin reuptake inhibition.

The surprisingly high potency of the (S,S) enantiomer over both the racemate and (R,R) reboxetine provides a treating physician an ability to prescribe an effective dosage of a norepinephrine reuptake inhibitor, *i.e.*, (S,S) reboxetine, that is about 10% to about 20% of the current daily dosage of reboxetine (racemate) to achieve the same reuptake inhibition at the norepinephrine site. In addition, the surprisingly high inhibition selectivity of an optically pure (S,S) reboxetine essentially limits inhibition to norepinephrine reuptake, thereby reducing adverse side effects associated with inhibiting the reuptake of serotonin.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

What is claimed is:

1. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, the method comprising the step of administering a therapeutically effective amount of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.
2. The method of claim 1 wherein said (S,S) reboxetine is administered in an amount of about 0.1 to about 10 mg/day.
3. The method of claim 2 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 8 mg/day.
4. The method of claim 3 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 5 mg/day.
5. The method of claim 4 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 2.5 mg/day.
6. The method of claim 5 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.9 mg/day.
7. The method of claim 6 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.8 mg/day.
8. The method of claim 7 wherein said (S,S) reboxetine is administered in an amount of about 0.5 to about 0.75 mg/day.

9. The method of claim 1 wherein said (S,S) reboxetine is administered orally, parenterally, transdermally, rectally, or vaginally.

10. The method of claim 9 wherein said (S,S) reboxetine is orally administered with a pharmaceutically acceptable carrier comprising at least one of a binder, diluent, lubricant, disintegrating agent, effervescent agent, dyestuff, sweetener, and wetting agent.

11. The method of claim 10 wherein the oral administration is by a sachet, capsule, tablet, or aerosol spray.

12. The method of claim 9 wherein said (S,S) reboxetine is parenterally administered subcutaneously, intravenously, or intramuscularly.

13. The method of claim 1, wherein the pharmaceutically acceptable salt is methanesulfonate.

14. The method of claim 1 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 90 wt.% of (S,S) reboxetine, and less than about 10 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

15. The method of claim 14 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 97 wt.% of (S,S) reboxetine and less than about 3 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

16. The method of claim 15 wherein the optically pure (S,S) reboxetine or pharmaceutically acceptable salt thereof comprises at least about 99 wt.% of (S,S) reboxetine and less than about 1 wt.% of (R,R) reboxetine, based on the total weight of reboxetine present.

17. The method of claim 1 wherein said condition is at least one of an addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, conduct disorder, cyclothymic disorder, depression, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, incontinence, an inhalation disorder, an intoxication disorder, migraine headaches, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, social phobia, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

18. The method of claim 17 wherein the addictive disorder comprises an addiction to at least one of alcohol, nicotine, and other psychoactive substances.

19. The method of claim 17 wherein the adjustment disorder comprises depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood.

20. The method of claim 17 wherein the age-associated learning and mental disorder comprises Alzheimer's disease.

21. The method of claim 17 wherein the depression comprises adolescent depression and minor depression.

22. The method of claim 17 wherein the premenstrual dysphoric disorder comprises premenstrual syndrome and late luteal phase dysphoric disorder.

23. The method of claim 17 wherein the psychotic disorder comprises schizophrenia, schizoaffective and schizophreniform disorders.

24. The method of claim 17 wherein social phobia comprises social anxiety disorder.

25. The method of claim 17 wherein the sleep disorder comprises narcolepsy and enuresis.

26. The method of claim 17 wherein somatoform disorders comprise somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS.

27. The method of claim 17 wherein incontinence comprises one or more of stress incontinence, genuine stress incontinence, and mixed incontinence.

28. The method of claim 17 wherein said condition is at least one of an adjustment disorder, an age-associated learning or mental disorder, apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, depression, dysthymic disorder, generalized anxiety disorder, nicotine addiction, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, and SSRJ "poop out" syndrome.

29. The method of claim 28 wherein said condition is at least one of apathy, attention-deficit hyperactivity disorder, attention-deficit disorder caused by medical conditions, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, depression, nicotine addiction, post-traumatic stress disorder, and SSRI "poop out" syndrome.

30. A method of treating a human suffering from a condition, or preventing said condition, wherein inhibiting reuptake of norepinephrine provides a benefit, while diminishing adverse side effects, the method comprising the steps of administering a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, to an individual, said optically pure (S,S) reboxetine being substantially free of (R,R) reboxetine.

31. The method of claim 30 wherein said adverse affects comprise dizziness, insomnia, lightheadedness, changes in blood pressure, sweating, gastrointestinal disturbances, sexual dysfunction in males, anticholinergic-like effects, and side effects with drug-drug interactions.

32. A method of treating or preventing a nervous system disorder comprising the step of administering a therapeutically effective dose of racemic reboxetine or a pharmaceutically acceptable salt thereof to an individual, wherein said disorder is at least one of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, incontinence, migraine headaches, obesity peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorders, a specific developmental disorders, and SSRI "poop out" syndrome.

33. The method of claim 32 wherein said disorder is at least one of an adjustment disorder, an age-associated learning or mental disorder, apathy, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, dysthymic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, and SSRI "poop out" syndrome.

34. The method of claim 33 wherein said disorder is at least one of apathy, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, post-traumatic stress disorder, and SSRI "poop out" syndrome.

35. The method of claim 32 wherein the reboxetine is administered to the individual in an amount of about 2 to about 10 mg/day.

36. The method of claim 35 wherein the reboxetine is administered to the individual in an amount of about 4 to about 10 mg/day.

37. The method of claim 36 wherein the reboxetine is administered to the individual in an amount of about 6 to about 10 mg/day.

38. The method of claim 32 wherein said reboxetine is administered orally, parenterally, transdermally, rectally, or vaginally.

39. The method of claim 38 wherein said reboxetine is orally administered with a pharmaceutically acceptable carrier comprising at least one of a binder, diluent, lubricant, disintegrating agent, effervescent agent, dyestuff, sweetener, and wetting agent.

40. The method of claim 39 wherein the oral administration is by a sachet, capsule, tablet, or aerosol spray.

41. The method of claim 38 wherein said reboxetine is parenterally administered subcutaneously, intravenously, or intramuscularly.

42. The method of claim 32 wherein the pharmaceutically acceptable salt is methanesulfonate.

43. A preparation of a medicament from a composition comprising reboxetine to treat or prevent at least one nervous system disorder selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, incontinence, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

44. Use of reboxetine in a manufacture of a medicament to treat or prevent at least one nervous system disorder selected from the group consisting of an adjustment disorder, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, incontinence, migraine headaches, obesity, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorders, and SSRI "poop out" syndrome.

ABSTRACT OF THE DISCLOSURE

Methods of treating humans suffering from, or preventing humans from suffering, depression, a mental, a behavioral, and/or a neurological condition where inhibiting reuptake of norepinephrine is a benefit are disclosed. The methods generally include administration of pharmaceutical compositions comprising reboxetine (2-[(2-ethoxyphenoxy)(phenyl)methyl]morpholine) or an optically pure (S,S) enantiomer thereof. Also disclosed are preparations of a medicament from a composition comprising reboxetine, and uses of reboxetine in a manufacture of the medicament to treat a human suffering from, or prevent a human from suffering, depression, a mental, a behavioral, and/or a neurological condition.

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 301

Radicación no 00-49691

Concepto Técnico no 628

Clasificación Internacional de Patentes A61K 31/535 // 31/075

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de **Patente de Invención**:

- SI ☒ NO ☐ Contiene un resumen de la invención (Art.26-e).
- SI ☒ NO ☐ Contiene el título o nombre de la invención (Art.27-d).
- SI ☒ NO ☐ Contiene la descripción de la invención (Art.26-b).
- SI ☒ NO ☐ NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art.26-d)
- SI ☒ NO ☐ Contiene una o más reivindicaciones. (Art.26-c).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
- SI ☐ NO ☒ La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI ☒ NO ☐ La prioridad coincide con la materia reivindicada.
- SI ☒ NO ☐ **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI ☐ NO ☐ ver hoja(s) anexa(s)

1. Se anexa nuevo capítulo reivindicatorio (Folio 62 y 63) que reemplaza al presentado originalmente.
2. Se envían los artes finales de la estructura química principal según lo requerido.
3. Se adjunta nuevo extracto para publicación y nueva tarjeta de archivo temático.

EXAMINADOR TÉCNICO

202040

Bogotá D. C., Abril 04, 2002.

Folio 302
416
2002-08-29

2020
Bogotá, D.C.

Doctor(a)
JOSÉ ANTONIO LLOREDA
Apoderado(a)

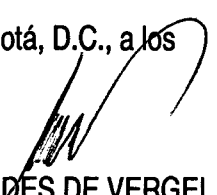
REFERENCIA:	Radicación No.	00-49691
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	913
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la comunidad andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase

Dado en Bogotá, D.C., a los

26 de mayo de 2002


ALIX CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, D.C., 04-05-05 El extracto de esta solicitud fue publicado en el número 519 de la Gaceta de Propiedad Industrial, de fecha 29-08-02. El término hábil señalado por la ley expiró el 26-11-02 y SI ☐ NO ☒ se presentaron oposiciones por parte de terceros.

202040

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 382 2695
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia