

Organización CSA Ltda



CSA047697



Industria y Comercio
SUPERINTENDENCIA

PGT

Monte

SUPERINTENDENCIA INDUSTRIAL
INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-97361

SOLICITUD DE PATENTE DE
INVENCION

TITULO: FORMA DE DOSIFICACIÓN NOVEDOSA

SOLICITANTE: GLAXO GROUP LIMITED

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford,
Middlesex UB6 ONN Inglaterra

APODERADO: CARLOS R. OLARTE

BOGOTÁ 10 de Septiembre de 2009

P2009/000159

Tado, No pago Ene de 2004
Fu. 01-10-2004



No. 09-097361- -00000-0000

Fecha: 2009-09-10 16:36:58 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 92

Industria y Comercio
SUPERINTENDENCIA

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT**

ENTRADA EN FASE NACIONAL

P2009/000159

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley
Avenue, Greenford Middlesex UB6 0NN

Nacionalidad o Domicilio: Británica

Lugar de Constitución: Inglaterra

Teléfono: _____ **Fax:** _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

**REPRESENTANTE
O APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747Bta
TP 74.295

**INVENTOR (ES)
(72)**

Nombre: 1) Alan James CLARKE; 2) David Geoffrey CULLINGFORD;
3) Yu LI

Dirección: 1) 1250 South Collegeville Road, P.O. Box 5089, Collegeville,
Pennsylvania 19426 E.U.A. 2) New Frontiers Science Park South, Third Avenue,
Harlow Essex CM19 5AW Gran Bretaña; 3) 1250 South Collegeville Road, P.O. Box
5089, Collegeville, Pennsylvania 19426 E.U.A.

Nacionalidad o Domicilio: 1) Estadounidense 2) Británica 3) China

5

PCT (86)

Solicitud Internacional No. PCT/EP2007/052430

Fecha Febrero 28, 2008

Publicación Internacional No. WO 2008/104590

Fecha Septiembre 4, 2008

6

Título (54) FORMA DE DOSIFICACIÓN NOVEDOSA (Folio 106)

Clasificación Internacional (51) A61K 9/00, A61K 9/20, A61K 9/50, A61K 31/55

Prioridad
SI ☒ NO ☐

(33) País de Origen
US

(32) Fecha
Marzo 1, 2007

(31) Número de Solicitud
60/892,267

9

Comprobante de pago No. 09-64,459

Fecha Agosto 31 de 2009



ANEXOS



Comprobante de pago de la tasa de presentación de la solicitud.



Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.



Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06-018 321



Documento de cesión del inventor al solicitante o a su causante. Declaración Regla 4.17



Declaraciones



Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).



Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).



Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).



Traducción del examen preliminar internacional efectuado por la IPEA.



De ser el caso, copia del contrato de acceso.



De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.



De ser el caso, certificado de depósito del material biológico.



Arte final 12 x 12.



De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.



De ser el caso, modificaciones efectuadas a la solicitud internacional.



Otros. Búsqueda Internacional



FIGURA CARACTERÍSTICA:



Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: 

C.C. 29.782.747 Btā T.P. 74.295

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-097361- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Fecha: 2009-09-10 16:36:58 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 92

NIT : 000000000

RECIBO OFICIAL DE CAJA : 09 - 64,459
FECHA : AGOSTO 31 DE 2009

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	33886436	31/08/2009	2,912,000.00

**** CONCEPTO ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	\$40,000.00
		TOTAL :	\$40,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del
Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE
GLAXO GROUP LIMITED

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de
agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario
autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos
exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del
5 de octubre de 1961 debe pasar por la sección consular de la Misión que
representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C


MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Ingle
Resolución No. 2117 del 7 O.

Yo, el infrascrito JAMES KERR MILLIGAN, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

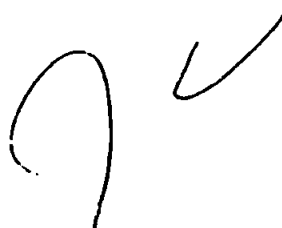
CERTIFICO:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don PETER JOHN GIDDINGS, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "GLAXO GROUP LIMITED", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número 305979, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don PETER JOHN GIDDINGS está debidamente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy trece de agosto del año dos mil tres.



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



6

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **James Kerr Milligan**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté
6. the/le 14 August 2003

5. at London/à Londres
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.
8. Number/sous No **G229474**
9. Stamp:
timbre:
10. Signature: **J. Garbrah**



[Handwritten signature]

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

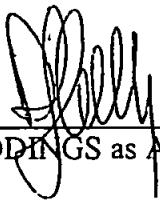
Poder

El suscrito,

domiciliado en

Glaxo Group Limited
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:


Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City/Country/Ciudad,País: Brentford, Middlesex, England

Sheet No

Box No. VIII(ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general and the specific Notes to Box No. VIII(ii)). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51 bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to international application No. PCT/EP2008/052430

GLAXO GROUP LIMITED is entitled to apply for and be granted a patent by virtue of the following:

- (i) transfer of entitlement from inventors **David Geoffrey CULLINGFORD** to GlaxoSmithKline Services Unlimited by way of employment contract
- (ii) an assignment from GlaxoSmithKline Services Unlimited to Glaxo Group Limited dated 1 March 2007
- (iii) an assignment from inventors **Allan James CLARKE; Yu LI** to Glaxo Group Limited dated 1 March 2007

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII(ii)".

Form PCT/RO/101 (declaration sheet (ii)) (March 2001; reprint January 2003)

See Notes to the request form

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



PCT

(43) International Publication Date
4 September 2008 (04.09.2008)

(10) International Publication Number
WO 2008/104590 A2

(51) International Patent Classification:

A61K 9/20 (2006.01) A61K 9/00 (2006.01)
A61K 9/50 (2006.01) A61K 31/55 (2006.01)

(21) International Application Number:

PCT/EP2008/052430

(22) International Filing Date:

28 February 2008 (28.02.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/892,267 1 March 2007 (01.03.2007) US

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CLARKE, Alan James [US/US]; GlaxoSmithKline, 1250 South Collegeville Road, P.O. Box 5089, Collegeville, Pennsylvania 19426 (US). CULLINGFORD, David Geoffrey [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). LI, Yu [CN/US]; GlaxoSmithKline, 1250 South Collegeville Road, P.O. Box 5089, Collegeville, Pennsylvania 19426 (US).

(74) Agents: THORNLEY, Rachel et al.; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- without international search report and to be republished upon receipt of that report

(54) Title: NOVEL DOSAGE FORM

(57) Abstract: The present invention relates to a novel dosage form, to a process for preparing the dosage form and to the use of the dosage form in the treatment of neurological and psychiatric disorders.

WO 2008/104590 A2

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NOVEL DOSAGE FORM

This invention relates to a novel dosage form, to a process for preparing the dosage form and to the use of the dosage form in medicine.

5

International Patent Application, Publication Number WO2004/056369 discloses certain benzazepine derivatives including 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone.

10 WO2004/056369 teaches that benzazepine derivatives may be formulated using standard techniques. However, no dosage form containing 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone is explicitly disclosed.

15 In a first aspect, the present invention provides a dosage form comprising:

- a) 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof;
- b) a stabiliser, which reduces degradation of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone in the dosage
- 20 form when compared to a dosage form lacking said stabiliser; and
- c) a pharmaceutically acceptable excipient.

The dosage form may be adapted for administration to the patient by any desired route of administration. For example, dosage forms include those adapted for (1)

25 oral administration such as tablets, capsules, caplets, pills, lozenges, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets and cachets; (2) parenteral administration such as sterile solutions, suspensions, implants and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal and vaginal administration such as suppositories, pessaries

30 and foams; (5) inhalation and intranasal administration such as dry powders, aerosols, suspensions, and solutions (sprays and drops); (6) topical administration such as creams, ointments, lotions, solutions, pastes, drops, sprays, foams and gels; (7) ocular such as drops, ointment, sprays, suspensions and inserts; and (8) buccal and sublingual administration such as lozenges,

35 patches, sprays, drops, chewing gums and tablets.

In the context of this invention, the term "pharmaceutically acceptable excipient" refers to any pharmaceutically acceptable material present in the dosage form other than 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-

40 pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and the stabiliser. Suitable pharmaceutically acceptable excipients will vary depending

11

upon the particular dosage form chosen and include diluents, binders, disintegrants and superdisintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavouring agents, flavour-masking agents, colouring agents, anticaking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, rate modifying agents, preservatives, surfactants. The skilled person will appreciate that certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation. Guidance on the selection of suitable pharmaceutically acceptable excipients is available from Remington's Pharmaceutical Sciences (Mack Publishing Company).

The dosage forms of the invention may be prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one embodiment, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof, a stabiliser and a diluent. Suitable diluents include saccharides (e.g. lactose, sucrose, dextrose), sugar alcohols (e.g. mannitol, sorbitol), starch (e.g. corn starch, potato starch and pregelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulphate and dibasic calcium phosphate. The dosage form may further comprise other conventional excipients such as binders, disintegrants, lubricants and glidants. Suitable binders include starch (e.g. corn starch, potato starch and pregelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, polyvinylpyrrolidone, and cellulose and its derivatives (e.g. ethylcellulose, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose). Suitable disintegrants include starches, cross-linked polyvinylpyrrolidone, sodium starch glucolate, croscarmellose, alginic acid and sodium carboxymethyl cellulose. Suitable lubricants include stearic acid, magnesium stearate and calcium stearate. Suitable glidants include talc or colloidal silicon dioxide. The oral solid dosage form may further comprise an outer coating which may have cosmetic or functional properties.

In a more particular aspect, the present invention provides a dosage form for oral administration comprising a carrier tablet, which carrier tablet is at least partially covered by a film comprising:

12

- a) 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof, and
b) a stabiliser that reduces degradation of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone in the dosage
5 form, when compared to a dosage form lacking said stabiliser.

In the context of this application, the term "carrier tablet" refers to a tablet that is substantially free of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or pharmaceutically acceptable salts thereof.
10 Typically, the tablet does not contain any therapeutic agent, although embodiments in which the carrier tablet contains one or more therapeutic agents are encompassed by the invention.

The composition of the carrier tablet is not important provided that it is
15 pharmaceutically acceptable. The carrier tablet must, however, be of an appropriate size and shape to function as a tablet for oral administration. Any type of tablet may be used, for example, those described in Remington, The Science and Practice of Pharmacy, 21st Edition, 2005 (Ed. D. B. Troy). In one embodiment, the carrier tablet is formed by conventional compression technology
20 and comprises up to 100% w/w diluent, or a mixture of diluents. Conventional diluents include saccharides (e.g. lactose, sucrose, dextrose), sugar alcohols (e.g. mannitol, sorbitol), starch (e.g. corn starch potato starch and pregelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulphate and dibasic calcium phosphate. The tablet may further comprise up to
25 100% w/w binder, or a mixture of binders. Suitable binders include starch (e.g. corn starch, potato starch and pre-gelatinised starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, polyvinylpyrrolidone, and cellulose and its derivatives (e.g. ethylcellulose, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose). Carrier tablets may
30 also contain other conventional excipients such as lubricants (e.g. stearic acid, magnesium stearate and calcium stearate) and glidants (e.g. talc or colloidal silicon dioxide). In one embodiment, lubricants and glidants are each present in an amount up to 10% w/w, more particularly up to 5% w/w. In another embodiment, substrates formed by injection moulding such as moulded tablets or
35 capsule shells may be used as carrier tablets. Suitable thermoplastic materials for injection moulding include hydroxypropylcellulose, ethylcellulose, methacrylates and polyvinyl acetate.

In one embodiment, the carrier tablet is a tablet comprising microcrystalline
40 cellulose (e.g. Avicel PH-102), pregelatinized starch (e.g. Starch 1500) and

13

magnesium stearate. In a more particular embodiment, the carrier tablet has the following composition:

Excipient	% w/w
Microcrystalline Cellulose (e.g. Avicel PH-102)	90
Pregelatinized starch (e.g. Starch 1500)	9
Magnesium Stearate	1

5 In an alternative embodiment, the carrier substrate may be formulated such that it disintegrates in the mouth when administered orally, a so called "orally disintegrating tablet" or "ODT" substrate. Alternatively, the carrier substrate may be formulated so as to disintegrate in water, a so called "fast-dissolve tablet" or "FDT" substrate.

10

The carrier tablet provides a substrate or support for the film. In one embodiment, the carrier tablets are coated to substantially prevent absorption of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof by the carrier tablets.

15

However, embodiments in which there is absorption of the 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof by the carrier tablets are encompassed by the invention.

20

Suitable coatings for carrier tablets include aqueous film coats such as those commercially available from Colorcon, for example, the Opadry® coatings ("OPADRY WHITE 00F18484" or "OPADRY WHITE YS-1-7003"). Other suitable coatings include Surelease® (ethylcellulose). The dosage form may alternatively be coated with a film of gastroresistant and enterosoluble polymeric material.

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Suitable polymeric materials include cellulose acetophthalate, cellulose acetopropionate, cellulose trimellitate and acrylic and methacrylic copolymers. Colourings can be added.

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In one embodiment, the carrier tablet is coated with a film coat to a 2-6% weight gain.

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It will be appreciated that, in embodiments where the carrier tablet is coated to substantially prevent absorption of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof, the film coat selected must not be soluble in the solvent used during the manufacturing process of the dosage form. For example, where an aqueous solvent system is used, an aqueous film coat (like an Opadry®) will

14

immediately disintegrate and a coating not soluble in water (e.g. Surelease® or Eudragit®) is appropriate.

5 In one embodiment, the film containing 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof only partially coats the carrier tablet. In a more particular embodiment, the carrier tablets are shaped to contain one or more recesses or depressions. In such embodiments, the film containing 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a
10 pharmaceutically acceptable salt thereof may be substantially present within the recess of the carrier tablet.

The dosage form and/or film that at least partially covers the carrier tablet comprises 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone (the "free base") or a pharmaceutically acceptable salt
15 thereof. In the context of this invention, reference to the free base or pharmaceutically acceptable salt encompasses solvates and hydrates of the free base or pharmaceutically acceptable salt.

20 1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone may be prepared according to known procedures, such as those disclosed in WO2004/056369. The disclosure of WO2004/056369 is incorporated herein by reference.

25 Pharmaceutically acceptable acid addition salts of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone include hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate,
30 methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) or hexanoate salts. Such salts can be formed by reaction with the appropriate acid, optionally in a suitable solvent such as an organic solvent, to give the salt which can be isolated for example by crystallisation and filtration.

35 The dosage form and/or the film may contain the free base, a pharmaceutically acceptable salt (stoichiometric or non-stoichiometric), or any mixture of these. In one embodiment, the dosage form contains the free base. In one embodiment, the film contains the free base.

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In one embodiment of the invention, the dosage form and/or the film contains between 1 µg and 1 mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone when measured as the amount of base present (that is, excluding any amount of acid added to form salts). In a more particular embodiment, the dosage form and/or the film contains between 1 µg and 200 µg, more particularly between 1 µg and 100 µg and even more particularly between 2 µg and 100 µg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone, when measured as the amount of free base present.

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The dosage form and/or the film additionally contains a pharmaceutically acceptable stabiliser that reduces degradation of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone (or a pharmaceutically acceptable salt thereof) in the dosage form containing the stabiliser when compared to a dosage form lacking the stabiliser. The degradation of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone (or a pharmaceutically acceptable salt thereof) in the dosage form can be analysed by measuring the total impurity/degradation product content of the dosage form using gradient HPLC, using the method described below. The skilled reader will appreciate that, with the exception of the presence or absence of stabiliser, the dosage forms should otherwise be comparable, and should have been stored under similar conditions for similar time periods.

In one embodiment, the mean total impurity/degradation product content calculated from at least 3 samples of the dosage form containing stabiliser stored for 1 month at 40°C, 75% relative humidity is at least 50% lower than the mean total impurity/degradation product content calculated from at least 3 samples of a comparable dosage form lacking said stabiliser that was stored under comparable conditions.

In another embodiment, the mean total impurity/degradation product content of at least 3 samples of the dosage form containing stabiliser when stored at 30°C, 65% relative humidity for a period of 3 months should not exceed 10%, more particularly 5%.

Certain pharmaceutically acceptable antioxidants may act as stabilisers in the context of the present invention. Pharmaceutically acceptable antioxidants include those described in The Handbook of Pharmaceutical Excipients, Third Edition, 2000 (Ed. A.H. Kibbe). In one embodiment, the stabiliser is selected from the group consisting of citric acid, malic acid, ascorbic acid and its salts,

16

sodium bicarbonate, butylated hydroxyanisole and butylated hydroxytoluene. Combinations of stabilisers may also be used in the present invention.

- 5 In one embodiment, the stabiliser is citric acid and, optionally butylated hydroxyanisole. In one embodiment, the film contains citric acid and, optionally butylated hydroxyanisole.

- 10 The stabiliser or stabilisers must be present in the dosage form and/or the film in a sufficient amount to reduce degradation of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof. In certain embodiments comprising citric acid, the molar ratio of free base to citric acid is in the range 1.5 : 1 to 1 : 500.

- 15 The film may additionally contain a film former, such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxyethylcellulose, carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, carrageenan (kappa iota or lambda), gelatin, polyethylene glycol, polyethylene oxide, pullulan or acrylic polymer (e.g. EUDRAGIT grades RL, RS, E, L, S, FS30D) or any combinations thereof. In one
20 embodiment, the film former is hydroxypropylcellulose. It will be apparent to the one skilled in the art, that any film former included in the dosage form should be soluble in the solvent used during its production.

- 25 The film may additionally contain other excipients. For example, it has been found that certain solvent systems, such as aqueous systems, require addition of surfactants (e.g. polysorbates (20, 40, 80), Triton 100, sodium lauryl sulphate or tyloxopol) and/or antifoaming agents (polydimethylsiloxane or dimethicone). Therefore, in a further embodiment, the film additionally contains one or more surfactants and/or one or more antifoaming agents.

- 30 The dosage form may be further coated. Suitable coatings include those listed above as suitable for coating of the carrier tablet. In one embodiment, the dosage form is coated to 2-6% weight gain.

- 35 The dosage form may optionally be packaged in a low oxygen environment. This may be achieved by inclusion of an oxygen scavenger in the packaging of the dosage form. Suitable oxygen scavengers include PharmaKeep® KH and KD (commercially available from Sud Chemie) and StabilOx™ speciality oxygen scavenger (commercially available from Multisorb Technologies). Alternatively,
40 the dosage forms can be packaged in bottles that are impermeable to oxygen.

Aluminium-aluminium blisters may also be used to package the dosage forms in a low oxygen environment.

5 In another aspect, the invention provides a method for preparing the dosage form of the invention. The method comprises dispensing a solution or suspension of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser onto a carrier tablet. Any solvent may be used provided that the stabiliser and any other excipients present in the film are soluble in the solvent. The solvent is typically
10 volatile, and must be pharmaceutically acceptable in the (residual) quantities in which it appears in the finished dosage form.

Suitable solvents include water, organic solvents, propellants, liquefied gases and volatile silicones. In one embodiment, the solution or suspension of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser is
15 prepared using an organic solvent, such as methanol, ethanol, acetone, acetic acid or methylene chloride. Mixtures of solvents (e.g. water-ethanol) may also be used. In one embodiment, the solvent is methanol.

20 In a further aspect, the invention provides a solution or suspension of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser in a solvent system. In one embodiment, the solution or suspension further
25 comprises one or more film formers and/or surfactants and/or antifoaming agents. In another embodiment, the solvent is an organic solvent, such as methanol, ethanol, acetone, acetic acid or methylene chloride, more particularly methanol.

30 In certain embodiments in which the stabiliser is citric acid, it is present in the solution or suspension in an amount between 2-3% w/v, particularly 3% w/v. In certain embodiments in which the stabiliser is butylated hydroxyanisole, it is present in the solution or suspension in an amount between 0.01-0.1% w/v, particularly 0.02% w/v.

35 In certain embodiments in which the film former is hydroxypropylcellulose, it is present in the solution or suspension in an amount between 4-6% w/v, particularly 4% w/v.

40 The carrier tablet and dispensed solution/suspension may be heated (e.g. in a forced air oven) to evaporate excessive liquid and result in the formation of a film

upon at least a part of the surface of the carrier tablet. The dosage form may then optionally be film coated according to methods known in the art.

5 The carrier tablet used in the method for preparing the dosage form may have a recess or depression that provides a basin for the solution or suspension of 1-{6-
[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-
pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser to land
after being dispensed. Typically, biconcave tablets having recesses on two faces
of the tablet are employed. The two recesses can be used to receive the solution
10 or suspension of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-
yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof
and stabiliser. Alternatively, one of the recesses can be used to receive a
solution or suspension of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-
7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof
15 and stabiliser, and the remaining recess can be used to receive a solution or
suspension of another therapeutic agent to produce a dosage form containing
two different therapeutic agents. In a further embodiment, solutions of different
therapeutic agents may be layered one on top of the other.

20 The dosage form of the present invention may be produced using the apparatus
described in WO2005/123569 which publication is herein incorporated in its
entirety. More particularly, the dosage form of the present invention may be
produced by an apparatus containing a dispensing module for accurately
dispensing a predetermined amount of the solution or suspension of 1-{6-[(3-
25 cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-
pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser onto the
carrier tablets. The apparatus may also have a holding member for holding the
carrier tablets, which may move continually along the apparatus as the
dispensing module dispenses the solution/suspension onto each of the carrier
30 tablets.

The apparatus may also have a drying system that dries or evaporates solvent
from the solution/suspension deposited on each of the carrier tablets. The
holding member may move continually along the apparatus as the drying system
35 dries the dosage on each of the carrier tablets. The drying system may dry the
dosage by use of heated air, infrared or microwave heating.

The apparatus may also have a coating system that applies a coating over the
dosage form. The coating system may have a pad printing device or a sprayer
40 that applies the coating to each of the carrier substrates. The holding member
may move continually along the apparatus as the coating system applies the

19

coating to each of the carrier tablets. The apparatus may also have a coating dryer that dries the coating on each of the carrier tablets.

5 It will be apparent that the apparatus described above could re-process carrier tablets any number of times in order to add solutions or suspensions of different therapeutic agents. Alternatively, the apparatus could have additional dispensing systems in series to add each of the solutions/suspensions to the carrier tablets.

10 1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone and its pharmaceutically acceptable salts thereof are H3 antagonists having useful therapeutic properties. More particularly, 1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone and its pharmaceutically acceptable salts are believed to be of
15 potential use in the treatment of neurological diseases including Alzheimer's disease, dementia (including Lewy body dementia and vascular dementia), age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, migraine, Parkinson's disease, multiple sclerosis (including fatigue), stroke, pain of neuropathic origin (including neuralgias, neuritis and back pain), inflammatory pain (including osteoarthritis, rheumatoid arthritis, acute inflammatory pain and
20 back pain) and sleep disorders (including hypersomnolence, excessive daytime sleepiness, narcolepsy, sleep deficits associated with Parkinson's disease and fatigue, especially in multiple sclerosis); psychiatric disorders including psychotic disorders (such as schizophrenia (particularly cognitive deficit of schizophrenia) and bipolar disorder), attention deficit hyperactivity disorder, depression
25 (including major depressive disorder), anxiety and addiction; and other diseases including obesity and gastro-intestinal disorders.

Accordingly, in a further aspect, the present invention provides the dosage form for use in therapy. More particularly, the invention provides the dosage form for
30 use in the treatment or prophylaxis of the above disorders, in particular neurological and psychiatric disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the
35 sufferer the dosage form of the present invention.

In another aspect, the invention provides the use of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a
40 pharmaceutically acceptable salt thereof in the manufacture of the dosage form of the invention for use in the treatment of the above disorders.

1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or its pharmaceutically acceptable salts may be used in combination with other therapeutic agents. When 1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof is intended for use in the treatment of Alzheimer's disease, it may be used in combination with medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be symptomatic agents, for example those known to modify cholinergic transmission such as M1 muscarinic receptor agonists or allosteric modulators, M2 muscarinic antagonists, acetylcholinesterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), nicotinic receptor agonists or allosteric modulators (such as $\alpha 7$ agonists or allosteric modulators or $\alpha 4\beta 2$ agonists or allosteric modulators), PPAR agonists (such as PPAR γ agonists), 5-HT $_4$ receptor partial agonists, 5-HT $_6$ receptor antagonists or 5HT1A receptor antagonists and NMDA receptor antagonists or modulators, or disease modifying agents such as β or γ -secretase inhibitors.

When 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof is intended for use in the treatment of narcolepsy, it may be used in combination with medicaments claimed to be useful as treatments for narcolepsy. Suitable examples of such other therapeutic agents include modafinil, armodafinil and monoamine uptake blockers.

When 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof is intended for use in the treatment of schizophrenia, it may be used in combination with medicaments claimed to be useful as treatments of schizophrenia including i) antipsychotics including typical antipsychotics (for example chlorpromazine, thioridazine, mesoridazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thiothixine, haloperidol, molindone and loxapine), atypical antipsychotics (for example clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, amisulpride and aripiprazole), glycine transporter 1 inhibitors and metabotropic receptor ligands; ii) drugs for extrapyramidal side effects, for example anticholinergics (such as benztropine, biperiden, procyclidine, and trihexyphenidyl) and dopaminergics (such as amantadine); iii) antidepressants including serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, paroxetine, dapoxetine and sertraline), dual serotonin/noradrenaline reuptake inhibitors (such as venlafaxine, duloxetine and milnacipran), noradrenaline reuptake inhibitors (such as reboxetine), tricyclic

21

antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline and trimipramine), monoamine oxidase inhibitors (such as isocarboxazide, moclobemide, phenelzine and tranylcypromine), and others (such as bupropion, mianserin, mirtazepine, nefazodone and trazodone); iv)
5 anxiolytics including benzodiazepines such as alprazolam and lorazepam; and v)
cognitive enhancers for example cholinesterase inhibitors (such as tacrine, donepezil, rivastigmine and galantamine).

10 The invention thus provides, in a further aspect, a dosage form comprising a carrier tablet which carrier tablet is at least partially coated by a film comprising 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and a stabiliser, which dosage form further comprises an additional therapeutic agent or agents.

15 It will be apparent that the additional therapeutic agent may be present in the carrier tablet. Alternatively, as discussed above, a film containing additional therapeutic agents may be deposited on the carrier tablet. Where the carrier tablet has two recesses, one recess may contain the film containing 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser, and the
20 second recess may contain the film containing the additional therapeutic agent or agents. Alternatively, the films containing 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser, and the additional therapeutic agent may
25 be layered one on top of the other.

When 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent active against the same disease
30 state the dose of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone (or its pharmaceutically acceptable salt) may differ from that when the 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone (or its pharmaceutically acceptable salt) is formulated alone. Appropriate doses will be readily appreciated by those skilled
35 in the art.

The following examples illustrate the invention but do not limit it in any way.

Examples

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22

Example 1: Preparation of round tablets containing 0.05mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone

- 5 The core components were passed through a nominal 30 mesh screen and then blended together in a suitable blender and compressed on a rotary tablet press to produce round biconcave tablets with a diameter of 9.525 mm and an approximately 0.8 mm deep trough on both sides of the tablet. Compression was followed by de-dusting and metal checking. The tablets were then transferred to a
10 coating pan and coated to a target 4% (w/w) gain.

The composition of the carrier tablets is given below:

Core

Component	Weight (mg)
Microcrystalline cellulose (Avicel PH-102)	210
Pregelatinized Starch (Starch 1500)	21
Magnesium Stearate	2.3
Total	233.3

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Film Coat

Component	Weight (mg)
Opadry White YS-1-7003	9.3
Purified Water	qs*
Total	242.6

*Removed during processing

- Carrier solution was prepared by dissolving 4 g hydroxypropyl cellulose (Grade EF; HPC), 2 g anhydrous citric acid and 0.02 g butylated hydroxyanisole (BHA) in
20 methanol, filtering through a 10 micron filter and then bringing the final volume to 100 ml with methanol.

- 1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone was dissolved in the carrier solution with a sonicator until a uniform
25 solution was obtained with a final concentration of 5 mg/g (w/w).

- 10 mg dosing solution was dispensed onto each tablet in an array of carrier tablets. The tablets were dried in a forced air oven at ~40°C for 10-20 minutes.

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The composition of the finished tablets is as follows:

Component	Weight (mg)
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1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone	0.05
Carrier (4% HPC/2% Citric acid/0.02% BHA in methanol*)	0.6
Carrier tablet	242.6
Total	243.3

* removed during manufacturing process

Examples 2-4: Preparation of round tablets containing 0.002 mg, 0.01 mg or 0.2 mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone

Tablets containing 0.002 mg, 0.01 mg or 0.2 mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone were prepared in the manner described in Example 1 except that the concentration of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone in the dosing solution was varied.

Example 5: Preparation of oval tablets containing 1 mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone

The core components were passed through a nominal 30 mesh screen and then blended together in a suitable blender and compressed on a rotary tablet press to produce oval biconcave tablets with dimensions of 15.9 mm x 8 mm x 3.4 mm with an approximately 0.9 mm trough on both sides. Compression was followed by de-dusting and metal checking. The tablets were then transferred to a coating pan and coated to a target 4% (w/w) gain.

The composition of the carrier tablets is given below:

Core

Component	Weight (mg)
Microcrystalline cellulose (Avicel PH-102)	286.2
Pregelatinized Starch (Starch 1500)	28.6
Magnesium Stearate	3.2
Total	318.0

Film Coat

Component	Weight (mg)
Opadry White 00F18484	12.7
Purified Water	qs*
Total	330.7

*Removed during processing

Carrier solution was prepared by dissolving 4 g hydroxypropyl cellulose (Grade EF; HPC), 2 g anhydrous citric acid and 0.02 g butylated hydroxyanisole (BHA) in methanol, filtering through a 10 micron filter and then bringing the final volume to 100 ml with methanol.

1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone was dissolved in the carrier solution with a sonicator until a uniform solution was obtained with a final concentration of 35 mg/g (w/w).

28.5 mg dosing solution was dispensed onto each tablet in an array of carrier tablets. The tablets were dried in a forced air oven at ~50°C for 10-20 minutes. If necessary or desirable, the drying temperature may be raised e.g. to ~60°C and/or the duration of drying may be increased in order to ensure adequate evaporation of solvent.

The composition of the finished tablets is as follows:

Component	Weight (mg)
1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone	1
Carrier (4% HPC/2% Citric acid/0.02% BHA in methanol*)	1.72
Carrier tablet	330.7
Total	333.42

* removed during manufacturing process

Example 6: Preparation of round tablets containing 0.01mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone

The core components were passed through a nominal 30 mesh screen and then blended together in a suitable blender and compressed on a rotary tablet press to produce round biconcave tablets with a diameter of 7.9 mm and an approximately 0.8 mm deep trough on both sides of the tablet. Compression was followed by de-dusting and metal checking. The tablets were then transferred to a coating pan and coated to a target 4% (w/w) gain.

The composition of the carrier tablets is given below:

Core

Component	Weight (mg)
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Microcrystalline cellulose (Avicel PH-102)	162
Pregelatinized Starch (Starch 1500)	16.2
Magnesium Stearate	1.8
Total	180

Film Coat

Component	Weight (mg)
Opadry White YS-1-7003	7.2
Purified Water	qs*
Total	187.2

*Removed during processing

- 5 Carrier solution was prepared by dissolving 5 g hydroxypropyl cellulose (Grade EF; HPC), and 3 g anhydrous citric acid in methanol, filtering through a 10 micron filter and then bringing the final volume to 100 ml with methanol.

- 10 1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone was dissolved in the carrier solution with a sonicator (and by also using a magnetic stirrer) until a uniform solution was obtained with a final concentration of 12.5 mg/g (w/w).

- 15 4 mg carrier solution was dispensed onto each tablet in an array of carrier tablets. The tablets were dried in a forced air oven at ~50°C for 10-20 minutes.

The composition of the finished tablets is as follows:

Component	Weight (mg)
1-{6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone	0.01
Carrier (5% HPC/3% Citric acid in methanol*)	0.4
Carrier tablet	187.2
Total	187.6

* removed during manufacturing process

- 20 **Examples 7-11: Preparation of round tablets containing 0.002 mg, 0.005 mg, 0.02mg, 0.05mg or 0.1 mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone**

- 25 Tablets containing 0.002 mg, 0.005 mg, 0.02 mg, 0.05mg or 0.1 mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone were prepared in the manner described in Example 6 except that

96

the concentration of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone in the carrier solution was varied.

5 The following examples (Example 12 and Example 13) are representative of an example tablet which may be prepared in accordance with the invention:

Example 12: Preparation of a Orally Disintegrating Tablet (ODT) Carrier Substrate

a) Preparation of ODT Carrier Substrate

10

StarLac and Neotame are passed through a nominal 20 mesh screen. The mixture and unsieved mint flavoring are transferred to a suitable blender and blended for approximately 10 minutes. Magnesium stearate is passed through a nominal 30 mesh screen, transferred to the blender and the entire mixture
15 blended for approximately 2 minutes. The weights of material used are calculated from the percentage weights given in Table A. The blend is compressed to meet the desired specifications (for example round, biconcave tablets, range in diameter from ~8 mm to ~9.5 mm) on a suitable rotary press utilizing appropriate tablet tooling. The tablets are passed through a de-duster and metal checker.

20

Table A

COMPOSITION	SPECIFICATION	% (w/w)	FUNCTION
StarLac*	Non Compendial	98.5%	Diluent
Mint Flavoring	Non Compendial	0.9%	Flavoring
Neotame	NF	0.1%	Sweetener
Magnesium Stearate	Ph. Eur/USP-NF/JP	0.5%	Lubricant

25 * StarLac: mixture of 85% alpha-lactose monohydrate (Ph. Eur./USP-NF) and 15% maize starch (Ph. Eur./USP-NF)

b) Preparation of ethylcellulose coat for application to tablet by Pad-Printing

30 Ethylcellulose is dissolved in methanol with stirring, and triethyl citrate added. The weights of material used are calculated from the percentage weights given in Table B. Sufficient methanol is added to bring to target on w/w basis. The solution is transferred to the ink cup of a pad printing machine equipped with a suitable image cliché with a round image, slightly smaller diameter than the
35 actual tablet diameter. A suitable polymer pad is installed to match the cliché image plate. Tablets are presented to the pad printer in a defined array,

matching the cliché. The pad printer may apply 2-4 tamps to the carrier tablet to apply a coat that will provide a protective layer to mitigate solvent infiltration into the uncoated carrier substrate during the liquid dispensing process.

5 Table B

COMPOSITION	SPECIFICATION	% (w/w)	FUNCTION
Ethylcellulose	NF	30	Protective barrier coat
Triethyl Citrate	Ph. Eur./USP-NF	1.67	Plasticiser
Methanol	Ph. Eur./USP-NF	qs*** to 100	vehicle

*** Methanol eliminated by evaporation.

10 **Example 13: Alternative preparation of an Orally Disintegrating Tablet (ODT) carrier substrate**

Mannitol, crospovidone XL, xylitol and Neotame are passed through a nominal 20 mesh screen, the mixture and the unsieved Mint Flavoring transferred to a suitable blender and blended for approximately 10 minutes. Magnesium stearate and colloidal silicon dioxide are passed through a nominal 30 mesh screen, transferred to the blender and the entire mixture blended for approximately 2 minutes. The weights of material used are calculated from the percentage weights given in Table C. The blend is compressed to meet the desired specifications (for example round, biconcave tablets, range in diameter from ~8 mm to ~9.5 mm) on a suitable rotary press utilizing an appropriate tablet tooling. The tablets are passed through a de-duster and metal checker.

An ethylcellulose coat may be prepared and applied as described for Example 12.

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Table C

COMPOSITION	SPECIFICATION	% (w/w)	FUNCTION
Mannitol (Grade 300 Direct Compression)	Ph. Eur/USP-NF/JP	73.15%	Diluent/sweetener
Crospovidone XL	Ph. Eur/USP-NF	20.00%	Disintegrant
Xylitol (Grade 300 for Direct Compression)	Ph. Eur/USP-NF/JP	5.00%	Diluent/sweetener
Mint Flavoring	Non Compendial	0.90%	Flavoring
Neotame	NF	0.10%	Sweetener

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Magnesium Stearate	Ph. Eur/USP-NF/JP	0.75%	Lubricant
Colloidal silicon dioxide	Ph. Eur/USP-NF/JP	0.10%	Lubricant

PROPERTIES: The stability of the drug substance in the tablets may be tested as set out below:

5

Dissolve 5 tablets in diluent (1:9 acetonitrile: 50 mM potassium dihydrogen orthophosphate, adjusted to pH 3 with orthophosphoric acid) to produce a final concentration of active agent of between 1-10 µg/ml and sonicate for 10 minutes. Check for complete disintegration and sonicate further if required. Allow to cool to ambient temperature and then centrifuge an aliquot of the sample at 14,000 rpm. Prepare samples using placebo tablets to act as control samples.

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Using the following instrument conditions, equilibrate the chromatographic system with 95% A, 5%B. Record the chromatograms for the sample and placebo preparations.

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Column: XBridge C18 3 µM 15 cm x 4.6 mm i.d.

Column Temperature: 40°C

Mobile Phase A: 10 mM ammonium bicarbonate, pH 10 with ammonia

Mobile Phase B: Acetonitrile

20

Flow Rate: 1 ml/min

Detector wavelength: 250 nm

Injection volume: 100 µl

Gradient Profile:

Time (min)	%A	%B
0	95	5
5	95	5
30	30	70
30.1	95	5

25

Following comparison of the chromatograms to identify impurities/degradation products, the percentage content of each impurity/degradation product in the control and sample injections can be calculated by dividing the area of the impurity/degradation product peak by the summed total of the peak for 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone and all impurities/degradation products, and multiplying by 100.

30

The total impurity/degradation product content can be calculated by summing the percentage content of each impurity/degradation product present. Typically, only impurities/degradation products present in an amount of greater than or equal to 0.05 or 0.03% are included in the calculation of total impurity/degradation product content.

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CLAIMS:

1. A dosage form comprising:
 - a) 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof;
 - b) a stabiliser, which reduces degradation of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone in the dosage form when compared to a dosage form lacking said stabiliser; and
 - c) a pharmaceutically acceptable excipient.
2. A dosage form according to claim 1 which comprises a carrier tablet, which carrier tablet is at least partially covered by a film comprising:
 - a) 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof, and
 - b) a stabiliser that reduces degradation of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone in the dosage form, when compared to a dosage form lacking said stabiliser.
3. A dosage form according to claim 1 or claim 2, which contains between 1 µg and 1 mg 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone, when measured as the amount of free base present.
4. A dosage form according to any preceding claim, which comprises 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone as a free base.
5. A dosage form according to any preceding claim, wherein said stabiliser is selected from the group consisting of citric acid, malic acid, ascorbic acid and its salts, sodium bicarbonate, butylated hydroxyanisole and butylated hydroxytoluene.
6. A dosage form according to claim 2, wherein said stabiliser is citric acid, and wherein the molar ratio of free base to citric acid is between 1.5 : 1 to 1 : 500.
7. A dosage form according to any preceding claim, wherein said carrier tablet has at least one recess.
8. A dosage form according to claim 7, wherein said film is present in a recess on said carrier tablet.

91

9. A dosage form according to any preceding claim, wherein there is substantially no absorption of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof by the carrier tablet.
- 5 10. A dosage form according to claim 9, wherein said carrier tablet is coated.
11. A dosage form according to any previous claim, wherein said dosage form is further coated.
- 10 12. A dosage form substantially as described in the examples.
13. A dosage form as described in examples 1-11.
- 15 14. A method of producing a dosage form as defined in claim 2, comprising dispensing a solution or suspension of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser onto a carrier tablet.
- 20 15. A method of treatment of neurological diseases which comprises administering to a host in need thereof a dosage form as defined in any one of claims 1 to 13.
- 25 16. Use of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof in the manufacture of a dosage form as defined in any one of claims 1 to 13 for the treatment of neurological diseases.
- 30 17. A dosage form as defined in any one of claims 1 to 13 for use in the treatment of neurological diseases.
- 35 18. A solution or suspension of 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and stabiliser in a solvent system.

32

FORMA DE DOSIFICACION NOVEDOSA

MEMORIA DESCRIPTIVA

5 La invención se refiere a una forma de dosificación novedosa, a un procedimiento para la preparación de la forma de dosificación y al uso de la forma de dosificación en medicina.

 Solicitud de Patente Internacional, Publicación Número WO2004/056369 describe ciertos derivados de benzazepina incluyendo 1-{6-
10 [(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona.

 WO2004/056369 muestra que los derivados de benzazepina se pueden formular usando técnicas estándar. Sin embargo, no se describe explícitamente una forma de dosificación que contiene 1-{6-[(3-ciclobutil-
15 2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona.

 En un primer aspecto, la presente invención provee una forma de dosificación que comprende:

- a) 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable;
- 20 b) un estabilizador, que reduce la degradación de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona en la forma de dosificación cuando se compara con una forma de dosificación que carece de dicho estabilizador; y

33

c) un excipiente farmacéuticamente aceptable.

La forma de dosificación se puede adaptar para administración al paciente mediante cualquier ruta de administración deseada. Por ejemplo, formas de dosificación incluyen aquellas adaptadas para (1) administración oral tal como tabletas, cápsulas, capletas, píldoras, grageas, polvos, sueros, 5 elíxires, suspensiones, soluciones, emulsiones, sacos y obleas; (2) administración parenteral tal como soluciones estériles, suspensiones, implantes y polvos para reconstitución; (3) administración transdérmica tal como parches transdérmicos; (4) administración rectal y vaginal tal como 10 supositorios, pesarios y espumas; (5) inhalación y administración intranasal tal como polvos secos, aerosoles, suspensiones y soluciones (pulverizadores y gotas); (6) administración tópica tal como cremas, ungüentos, lociones, soluciones, pastas, gotas, pulverizadores, espumas y geles; (7) ocular tal como gotas, ungüento, pulverizadores, suspensiones y suplementos; y (8) 15 administración bucal y sublingual tal como grageas, parches, pulverizadores, gotas, gomas masticables y tabletas.

En el contexto de esta invención, el término "excipiente farmacéuticamente aceptable" se refiere a cualquier material farmacéuticamente aceptable presente en la forma de dosificación diferente 20 de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y el estabilizador. Excipientes farmacéuticamente aceptables adecuados variarán dependiendo de la forma de dosificación particular elegida e incluyen diluyentes,

aglutinantes, desintegrantes y superdesintegrantes, lubricantes, deslizantes, agentes de granulación, agentes de recubrimiento, agentes humectantes, solventes, co-solventes, agentes de suspensión, emulsionantes, edulcorantes, agentes saborizantes, agentes de enmascaramiento del sabor, agentes colorantes, agentes anti-formación de torta, humectantes, agentes de quelación, plastificantes, agentes de incremento de viscosidad, agentes de modificación de velocidad, preservativos, agentes tensioactivos. La persona con experiencia en la técnica apreciará que ciertos excipientes farmacéuticamente aceptables puedan servir con más de una función y pueden servir con funciones alternativas dependiendo de que tanto de excipiente esté presente en la formulación y que otros ingredientes están presentes en la formulación. La guía en la selección de excipientes farmacéuticamente aceptables está disponible de Remington's Pharmaceutical Sciences (Mack Publishing Company).

Las formas de dosificación de la invención se pueden preparar usando técnicas y métodos conocidos por aquellos con experiencia en la técnica. Algunos de los métodos comúnmente usados conocidos en la técnica se describen en Remington's Pharmaceutical Sciences (Mack Publishing Company).

En una modalidad, la invención se refiere a una forma de dosificación oral sólida tal como una tableta o cápsula que comprende 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable, un estabilizador y un

diluyente. Diluyentes adecuados incluyen sacáridos (por ejemplo, lactosa, sucrosa, dextrosa), alcoholes de azúcar (por ejemplo, manitol, sorbitol), almidón (por ejemplo, almidón de maíz, almidón de papa y almidón pregelatinizado), celulosa y sus derivados (por ejemplo, celulosa microcristalina), sulfato de calcio y fosfato de calcio dibásico. La forma de dosificación además puede comprender otros excipientes convencionales tal como aglutinantes, desintegrantes, lubricantes y deslizantes. Aglutinantes adecuados incluyen almidón (por ejemplo, almidón de maíz, almidón de papa y almidón pregelatinizado), gelatina, acacia, alginato de sodio, ácido algínico, tragacanto, goma guar, polivinilpirrolidona, y celulosa y sus derivados (por ejemplo, etilcelulosa, metilcelulosa, carboximetilcelulosa, hidroxipropilcelulosa e hidroxipropilmetilcelulosa). Desintegrantes adecuados incluyen almidón, polivinilpirrolidona entrelazada, glucolato almidón de sodio, croscarmelosa, ácido algínico y carboximetilcelulosa de sodio. Lubricantes adecuados incluyen ácido esteárico, estearato de magnesio, y estearato de calcio. Deslizantes adecuados incluyen talco o dióxido de silicio coloidal. La forma de dosificación sólida oral además puede comprender un recubrimiento externo que puede tener propiedades cosméticas o funcionales.

En un aspecto más particular, la presente invención provee una forma de dosificación para administración oral que comprende una tableta portadora, cuya tableta portadora está al menos parcialmente cubierta por una película que comprende:

a) 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-

zb

3-piridinil}-2-pirrolidona o su sal farmacéuticamente aceptable, y

- b) un estabilizador que reduce la degradación de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona en la forma de dosificación, cuando se compara con una forma de dosificación que carece de dicho estabilizador.

En el contexto de esta solicitud, el término "tableta portadora" se refiere a una tableta que está sustancialmente libre de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o sus sales farmacéuticamente aceptables. Usualmente, la tableta no contiene algún agente terapéutico, aunque modalidades en las cuales la tableta portadora contiene uno o más agentes terapéuticos se incluyen por la invención.

La composición de la tableta portadora no es importante siempre y cuando sea farmacéuticamente aceptable. La tableta portadora debe, sin embargo, ser de un tamaño y forma apropiada para funcionar como una tableta para administración oral. Cualquier tipo de tableta se puede usar, por ejemplo, aquella descrita en Remington, The Science and Practice of Pharmacy, 21a edición, 2005 (Ed. D.B. Troy). En una modalidad, la tableta portadora se forma por tecnología de compresión convencional y comprende hasta el 100% p/p de diluyente, o una mezcla de diluyentes. Diluyentes convencionales incluyen sacáridos (por ejemplo, lactosa, sucrosa, dextrosa), alcoholes de azúcar (por ejemplo, manitol, sorbitol), almidón (por ejemplo, almidón de maíz, almidón de papa y almidón pregelatinizado), celulosa y sus derivados (por ejemplo, celulosa microcristalina), sulfato de calcio y fosfato de

calcio dibásico. La tableta además puede comprender hasta 100% p/p de aglutinante o una mezcla de aglutinantes. Aglutinantes adecuados incluyen almidón (por ejemplo, almidón de maíz, almidón de papa y almidón pregelatinizado), gelatina, acacia, alginato de sodio, ácido algínico, tragacanto, goma guar, polivinilpirrolidona, y celulosa y sus derivados (por ejemplo, etilcelulosa, metilcelulosa, carboximetilcelulosa, hidroxipropilcelulosa, e hidroxipropilmetilcelulosa). Tabletas portadoras también pueden contener otros excipientes convencionales tales como lubricantes (por ejemplo, ácido esteárico, estearato de magnesio y estearato de calcio), y deslizantes (por ejemplo, talco o dióxido de silicio coloidal). En una modalidad, cada uno de los lubricantes y deslizantes está presente en una cantidad de hasta 10% p/p, más particularmente hasta 5% p/p. En otra modalidad, sustratos formados mediante moldeado por inyección tal como tabletas moldeadas o cubiertas de cápsulas se pueden usar como tabletas portadoras. Materiales termoplásticos adecuados para moldeado por inyección incluyen hidroxipropilcelulosa, etilcelulosa, metacrilatos y acetato de polivinilo.

En una modalidad, la tableta portadora es una tableta que comprende celulosa microcristalina (por ejemplo, Avicel PH-102), almidón pregelatinizado (por ejemplo, Almidón 1500) y estearato de magnesio. En una modalidad más particular, la tableta portadora tiene la siguiente composición:

Excipiente	% p/p
Celulosa microcristalina (por ejemplo, Avicel PH-102)	90
Almidón pregelatinizado (por ejemplo, almidón 1500)	9
Estearato de magnesio	1

En una modalidad alternativa, el sustrato portador se puede formular de tal manera que se desintegre en la boca cuando se administre oralmente, un sustrato llamado "tableta desintegrante oralmente" u "ODT". De manera alternativa, el sustrato portador se puede formular entonces para desintegrarse en agua, un sustrato llamado "tableta de rápida disolución" o "FDT".

La tableta portadora provee un sustrato o soporte para la película. En una modalidad, las tabletas portadoras se recubren para prevenir sustancialmente la absorción de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable por las tabletas portadoras. Sin embargo, modalidades en las cuales existe absorción de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable por las tabletas portadoras se incluyen por la invención.

Recubrimientos adecuados para tabletas portadoras incluyen cubiertas de películas acuosas tales como aquellas comercialmente disponibles de Colorcon, por ejemplo, recubrimientos Opadry® ("OPADRY WHITE 00F18484" u "OPADRY WHITE YS-1-7003"). Otros recubrimientos adecuados incluyen Surelease® (etilcelulosa). La forma de dosificación alternativamente se puede recubrir con una película de material polimérico gastro-resistente y entero-soluble. Materiales poliméricos adecuados incluyen acetofalato de celulosa, acetopropionato de celulosa, trimelitato de celulosa y copolímeros acrílicos y metacrílicos. Se pueden añadir colorantes.

En una modalidad, la tableta portadora se recubre con una cubierta de película a un 2-6% de ganancia en peso.

Será apreciado que, en las modalidades donde la tableta portadora se recubre para prevenir sustancialmente la absorción de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable, la cubierta de película seleccionada no debe ser soluble en el solvente usado durante el procedimiento de fabricación de la forma de dosificación. Por ejemplo, cuando se usa un sistema de solvente acuoso, una cubierta de película acuosa (tipo un Opadry®) se desintegrará inmediatamente y un recubrimiento no soluble en agua (por ejemplo, Surelease ® o Eudragit®) es apropiado.

En una modalidad, la película que contiene 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable cubre sólo parcialmente la tableta portadora. En una modalidad más particular, las tabletas portadoras se forman para contener uno o más huecos o depresiones. En dichas modalidades, la película que contiene 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable puede estar presente sustancialmente dentro del hueco de la tableta portadora.

La forma de dosificación y/o película que cubre al menos parcialmente la tableta portadora comprende 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona (la "base libre") o su sal farmacéuticamente aceptable. En el contexto de esta invención, la

referencia a la base libre o sal farmacéuticamente aceptable incluye solvatos e hidratos de la base libre o sal farmacéuticamente aceptable.

1-{6-[(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona se puede preparar de acuerdo con procedimientos conocidos, tales como aquellos descritos en WO2004/056369. La descripción
5 de WO2004/056369 se incorpora aquí para referencia.

Sales de adición ácida farmacéuticamente aceptables de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona incluyen sales de bromhidrato, clorhidrato, sulfato, nitrato, fosfato, succinato, maleato, formiato, acetato, propionato, fumarato, citrato, tartrato,
10 lactato, benzoato, salicilato, glutamato, aspartato, p-toluenosulfonato, bencenosulfonato, metanosulfonato, etanosulfonato, naftalenosulfonato (por ejemplo, 2-naftalenosulfonato) o hexanoato. Dicha's sales se pueden formar mediante la reacción con el ácido apropiado, opcionalmente en un solvente
15 adecuado tal como un solvente orgánico, para proporcionar la sal que se puede asilar por ejemplo mediante cristalización y filtración.

La forma de dosificación y/o película puede contener la base libre, una sal farmacéuticamente aceptable (estequiométrica o no estequiométrica), o cualquier mezcla de estos. En una modalidad, la forma de dosificación contiene la base libre. En una modalidad, la película contiene la
20 base libre.

En una modalidad de la invención, la forma de dosificación y/o la película contiene entre 1 µg y 1 mg de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-

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3-benzazepin-7-il)oxi]-3-piridinil)-2-pirrolidinona cuando se mide como la cantidad de base presente (esto es, excluyendo cualquier cantidad de ácido añadido para formar sales). En una modalidad más particular, la forma de dosificación y/o la película contiene entre 1 µg y 200 µg, más particularmente entre 1 µg y 100 µg de aún más particularmente entre 2 µg y 100 µg de 1-{6-
5 [(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil)-2-pirrolidinona, cuando se mide como la cantidad de la base libre presente.

La forma de dosificación y/o la película contiene adicionalmente un estabilizador farmacéuticamente aceptable que reduce la degradación de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil)-2-
10 pirrolidinona (o su sal farmacéuticamente aceptable) en la forma de dosificación que contiene el estabilizador cuando se compara con una forma de dosificación que carece del estabilizador. La degradación de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil)-2-pirrolidinona
15 (o su sal farmacéuticamente aceptable) en la forma de dosificación se puede analizar al medir el contenido de impureza total/producto de degradación de la forma de dosificación usando HPLC de gradiente, usando el método descrito posteriormente. El lector con experiencia apreciará que, con la excepción de la presencia o ausencia del estabilizador, las formas de dosificación de otra
20 manera deben ser comparables, y deben ser almacenadas bajo condiciones similares por periodos de tiempo similares.

En una modalidad, el contenido de impureza total/producto de degradación medio calculado de al menos 3 muestras de la forma de

dosificación que contiene estabilizador almacenado durante 1 mes a 40°C, 75% de humedad relativa es al menos 50% menor que el contenido de impureza total/producto de degradación medio calculado de al menos 3 muestras de una forma de dosificación comparable que carece de dicho estabilizador que se almacena bajo condiciones comparables.

En otra modalidad, el contenido de impureza total/producto de gradación medio de la menos 3 muestras de la forma de dosificación que contiene estabilizador cuando se almacena a 30°C, 65% de humedad relativa por un periodo de 3 meses no debe exceder 10%, más particularmente 5%.

Ciertos antioxidantes farmacéuticamente aceptables pueden actuar como estabilizadores en el contexto de la presente invención. Antioxidantes farmacéuticamente aceptables incluyen aquellos descritos en The handbook of pharmaceutical excipients, tercera edición, 2000 (Ed. A.H. Kibbe). En una modalidad, el estabilizador se selecciona del grupo que consiste de ácido cítrico, ácido málico, ácido ascórbico y sus sales, bicarbonato de sodio, hidroxianisol butilado e hidroxitolueno butilado. Combinaciones de estabilizadores también se pueden usar en la presente invención.

En una modalidad, el estabilizador es ácido cítrico y, opcionalmente hidroxianisol butilado. En una modalidad, la película contiene ácido cítrico y opcionalmente hidroxianisol butilado.

El estabilizador o estabilizadores pueden estar presentes en la forma de dosificación y/o la película en una cantidad suficiente para reducir la

degradación de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable. En ciertas modalidades que comprenden ácido cítrico, la relación molar de base libre a ácido cítrico en el intervalo de 1.5:1 a 1:500.

5 La película puede contener adicionalmente una sustancia formadora de película, tal como hidroxipropilcelulosa, hidroxipropilmetil celulosa, hidroxietilcelulosa, carboximetil celulosa, alcohol polivinílico, polivinil pirrolidona, carragenano (kappa iota o lambda), gelatina, polietilenglicol, óxido de polietileno, pululano o polímero acrílico (por ejemplo, EUDRAGIT grados
10 RL, RS, E, L, S, FS30D) o cualquier combinación de los mismos. En una modalidad, la sustancia formadora de película es hidroxipropilcelulosa. Será aparente para una persona con experiencia en la técnica, que cualquier sustancia formadora de película incluida en la forma de dosificación debe ser soluble en el solvente usado durante su producción.,

15 La película adicionalmente puede contener otros excipientes. Por ejemplo, se ha encontrado que ciertos sistemas de solvente, tal como sistemas acuosos, requieren la adición de agentes tensioactivos (por ejemplo, polisorbatos (20, 40, 80), Triton 100, lauril sulfato de sodio o tiloxopol) y/o agentes anti-espumantes (polidimetilsiloxano o dimeticona). Por lo tanto, en
20 una modalidad adicional, la película contiene adicionalmente uno o más agentes tensioactivos y/o uno o más agentes anti-espumantes.

La forma de dosificación puede ser además recubierta. Recubrimientos adecuados incluyen aquellos enlistados anteriormente como

sea adecuado para el recubrimiento de la tableta portadora. En una modalidad, la forma de dosificación es recubierta a 2-6% en peso de ganancia.

La forma de dosificación puede opcionalmente ser envasada en un ambiente con poco oxígeno. Esto se puede lograr mediante la inclusión de un depurador de oxígeno en el envasado de la forma de dosificación. Depuradores de oxígeno adecuados incluyen PharmaKeep® KH y KD (comercialmente disponible de Sud Chemie) y StabilOx™ especialmente depurador de oxígeno (comercialmente disponible de Multisorb Technologies). De manera alternativa, las formas de dosificación se pueden envasar en botellas que son impermeables al oxígeno.

Envases tipo burbuja de aluminio-aluminio también se pueden usar para envasar las formas de dosificación en un ambiente con poco oxígeno.

En otro aspecto, la invención provee un método de preparación de la forma de dosificación de la invención. El método comprende la dispensación de una solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y estabilizador en una tableta portadora. Se puede usar cualquier solvente siempre y cuando el estabilizador y cualquiera de los otros excipientes presentes en la película sean solubles en el solvente. El solvente es usualmente volátil, y debe ser farmacéuticamente aceptable en las cantidades (residuales) en las cuales aparece en la forma de dosificación terminada.

Solventes adecuados incluyen agua, solventes orgánicos, propelentes, gases licuados y siliconas volátiles. En una modalidad, la solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente
5 aceptable y estabilizador se preparan usando un solvente orgánico, tal como metanol, etanol, acetona, ácido acético o cloruro de metileno. Mezclas de solventes (por ejemplo, agua-etanol) también se pueden usar. En una modalidad, el solvente es metanol.

En un aspecto adicional, la invención provee una solución o
10 suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y estabilizador en un sistema de solvente. En una modalidad, la solución o suspensión comprende adicionalmente uno o más sustancias formadoras de película y/o agentes tensioactivos y/o agentes anti-espumado. En otra modalidad, el
15 solvente es un solvente orgánico, tal como metanol, etanol, acetona, ácido acético o cloruro de metileno, más particularmente metanol.

En ciertas modalidades en las cuales el estabilizador es ácido cítrico, está presente en la solución o suspensión en una cantidad entre 2-3% p/v, particularmente 3% p/v. En ciertas modalidades en las cuales el
20 estabilizador es hidroxianisol butilado, está presente en la solución o suspensión en una cantidad entre 0.01-0.1% p/v, particularmente 0.02% p/v.

En ciertas modalidades en las cuales la sustancia formadora de película es hidroxipropilcelulosa, está presente en la solución o suspensión en

46

una cantidad entre 4-6% p/v, particularmente 4% p/v.

La tableta portadora y solución/suspensión dispensada se puede calentar (por ejemplo, en un horno de aire forzado) para evaporar líquido excesivo y resultando en la formación de una película durante al menos una parte de la superficie de la tableta portadora. La forma de dosificación entonces puede opcionalmente ser recubierta con película de acuerdo con métodos conocidos en la técnica.

La tableta portadora usada en el método para la preparación de la forma de dosificación puede tener un hueco o depresión que provee una cápsula para la solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y el estabilizador para descargarse después de ser dispensada. Usualmente, las tabletas biconcavas que tienen huecos en dos caras de las tabletas se emplean. Los dos huecos se pueden usar para recibir la solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y estabilizador. De manera alternativa, uno de los huecos se puede usar para recibir una solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y el estabilizador, y el hueco restante se puede usar para recibir una solución o suspensión de otro agente terapéutico para producir una forma de dosificación que contiene dos diferentes agentes terapéuticos. En una modalidad adicional, soluciones de diferentes agentes

terapéuticos se pueden formar en capas una en la parte superior de la otra.

La forma de dosificación de la presente invención se puede producir usando el aparato descrito en WO2005/123569 cuya publicación se incorpora aquí en su totalidad. Más particularmente, la forma de dosificación

5 de la presente invención se puede producir por un aparato que contiene un módulo de dispensación para dispensar de manera exacta una cantidad predeterminada de la solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-

tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y el estabilizador en las tabletas portadoras. El

10 aparato también puede tener un miembro de retención para retener las tabletas portadoras, que puede moverse continuamente a lo largo del aparato conforme el módulo de dispensación dispensa la solución/suspensión en cada una de las tabletas portadoras.

El aparato también puede tener un sistema de secado que seca

15 o evapora el solvente de la solución/suspensión depositada en cada una de las tabletas portadoras. El miembro de retención puede moverse continuamente a lo largo del aparato conforme el sistema de secado seca la dosificación en cada una de las tabletas portadoras. El sistema de secado puede secar la dosificación mediante el uso de aire calentado, calentamiento

20 con infrarrojo o en microondas.

El aparato puede tener también un sistema de recubrimiento que aplica un recubrimiento sobre la forma de dosificación. El sistema de recubrimiento puede tener un dispositivo de impresión indirecta de

huecograbado o un pulverizador que aplica el recubrimiento a cada uno de los sustratos portadores. El miembro de retención puede moverse continuamente a lo largo del aparato conforme el sistema de recubrimiento aplica el recubrimiento a cada una de las tabletas portadoras. El aparato también
5 puede tener un secador de recubrimiento que seca el recubrimiento en cada una de las tabletas portadoras.

Será aparente que el aparato descrito anteriormente puede re-procesar las tabletas portadoras cualquier número de veces a fin de añadir soluciones o suspensiones de diferentes agentes terapéuticos. De manera
10 alternativa, el aparato puede tener sistemas de dispensación adicionales en serie para añadir cada una de las soluciones/suspensiones a las tabletas portadoras.

1-{6-[(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona y sus sales farmacéuticamente aceptables son
15 antagonistas H₃ que tienen propiedades terapéuticas útiles. Más particularmente, 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona y sus sales farmacéuticamente aceptables se cree que son de uso potencial en el tratamiento de enfermedades neurológicas que incluyen enfermedad de Alzheimer, demencia (incluyendo demencia de
20 cuerpos de Lewy y demencia vascular), disfunción de memoria relacionada con la edad, deterioro cognitivo medio, déficit cognitivo, epilepsia, migraña, enfermedad de Parkinson, esclerosis múltiple (incluyendo fatiga), apoplejía, dolor de origen neuropático (incluyendo neuralgias, neuritis y dolor de

49

5 espalda), dolor inflamatorio (incluyendo osteoartritis, artritis reumatoide, dolor inflamatorio agudo y dolor de espalda) y trastornos de sueño (incluyendo hipersomnolencia, somnolencia durante el día excesiva, narcolepsia, déficits de sueño asociados con enfermedad de Parkinson y fatiga, especialmente en

5 esclerosis múltiple); trastornos psiquiátricos incluyendo trastornos psicóticos (tal como esquizofrenia (particularmente déficit cognitivo de esquizofrenia) y trastorno bipolar), trastorno de hiper-actividad por déficit de atención, depresión (incluyendo trastorno depresivo mayor), ansiedad y adicción; y otras enfermedades incluyendo obesidad y trastornos gastrointestinales.

10 En consecuencia, en un aspecto adicional, la presente invención provee la forma de dosificación para uso en terapia. Más particularmente, la invención provee la forma de dosificación para el uso en el tratamiento o profilaxis de los trastornos anteriores, en particular trastornos neurológicos y psiquiátricos.

15 La invención además provee un método de tratamiento o profilaxis de los trastornos anteriores, en mamíferos incluyendo humanos, que comprende la administración al que padece de la forma de dosificación de la presente invención.

20 En otro aspecto, la invención provee el uso de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona y su sal farmacéuticamente aceptable en la fabricación de la forma de dosificación de la invención para el uso en el tratamiento de los trastornos anteriores.

1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-

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piridinil}-2-pirrolidinona o sus sales farmacéuticamente aceptables se pueden
usar en combinación con otros agentes terapéuticos. Cuando 1-{6-[(3-
ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona
o su sal farmacéuticamente aceptable se destina para el uso en el tratamiento
5 de enfermedad de Alzheimer, se puede usar en combinación con
medicamentos reclamados por ser útiles como tratamientos de modificación
de enfermedad o sintomáticos de la enfermedad de Alzheimer. Ejemplos
adecuados de dichos otros agentes terapéuticos pueden ser agentes
sintomáticos, por ejemplo aquellos conocidos para modificar la transmisión
10 colinérgica tal como agonistas del receptor muscarínico M1 o moduladores
alostéricos, antagonistas muscarínicos M2, inhibidores de acetilcolinesterasa
(tal como tetrahidroaminoacridina, clorhidrato de donepezilo, y rivastigmina),
agonistas del receptor nicotínico o moduladores alostéricos (tales como
agonistas $\alpha 7$ o moduladores alostéricos o agonistas $\alpha 4\beta 2$ o moduladores
15 alostéricos), agonistas de PPAR (tal como agonistas de PPAR γ), agonistas
parciales del receptor 5-HT $_4$, antagonistas del receptor 5-HT $_6$ o antagonistas
del receptor 5HT1A y antagonistas o moduladores del receptor NMDA, o
agentes de modificación de enfermedad tal como inhibidores de β o γ -
secretasa.

20 Cuando 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-
il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable se
destina para el uso en el tratamiento de narcolepsia, se puede usar en
combinación con medicamentos reclamados por ser útiles como tratamientos

91

de narcolepsia. Ejemplos adecuados de dichos agentes terapéuticos diferentes incluyen bloqueadores de captación de modafinil, armodafinil y monoamina.

Cuando 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable se
5 destina para el uso en el tratamiento de esquizofrenia, se puede usar en combinación con medicamentos reclamados por ser útiles como tratamientos de esquizofrenia incluyendo i) antipsicóticos incluyendo antipsicóticos usuales (por ejemplo clorpromazina, tioridazina, mesoridazina, flufenazina, perfenazina,
10 proclorperazina, trifluoperazina, tiotixina, haloperidol, molindona y loxapina), antipsicóticos atípicos (por ejemplo, clozapina, olanzapina, risperidona, quetiapina, aripirazol, ziprasidona, amisulprida y aripiprazol), inhibidores del transportador de glicina 1 y ligandos del receptor metabotrópico; ii) fármacos para efectos secundarios extrapiramidales, por ejemplo anticolinérgicos (tal
15 como benztropina, biperiden, procilidina, y trihexifenidilo) y dopaminérgicos (tal como amantadina); iii) antidepresivos incluyendo inhibidores de recaptación de serotonina (tal como citalopram, escitalopram, fluoxetina, paroxetina, dapoxetina y sertralina), inhibidores de recaptación de serotonina/noradrenalina dobles (tal como venlafaxina, duloxetina y
20 milnacipran), inhibidores de recaptación de noradrenalina (tal como reboxetina), antidepresivos tricíclicos (tal como amitriptilina, clomipramina, imipramina, maprotilina, nortriptilina y trimipramina), inhibidores de monoamina oxidasa (tal como isocarboxazida, moclobemida, fenelzina, y

52

tranilcipromina), y otros (tal como bupropion, mianserin, mirtazepina, nefazodona y trazodona); iv) ansiolíticos incluyendo benzodiazepinas tal como alprazolam y lorazepam; y v) intensificadores cognitivos por ejemplo, inhibidores de colinesterasa (tal como tacrina, donepezil, rivastigmina y galantamina).

La invención de esta manera provee, en un aspecto adicional, una forma de dosificación que comprende una tableta portadora cuya tableta portadora es al menos parcialmente recubierta por una película que comprende 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y un estabilizador, cuya forma de dosificación además comprende un agente o agentes terapéuticos adicionales.

Será aparente que el agente terapéutico adicional puede estar presente en la tableta portadora. De manera alternativa, como se discutió anteriormente, una película que contiene agentes terapéuticos adicionales se pueden depositar en la tableta portadora. Cuando la tableta portadora tiene dos huecos, un hueco puede contener la película que contiene 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y estabilizador, y el segundo hueco puede contener la película que contiene el agente o agentes terapéuticos adicionales. De manera alternativa, las películas que contienen 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y estabilizador, y el agente terapéutico



adicional puede estar en forma de capas una en la parte superior de la otra.

Cuando 1-{6-[(3-ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable se usa en combinación con un segundo agente terapéutico activo contra el mismo estado de enfermedad, la dosis de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona (o su sal farmacéuticamente aceptable) puede diferir de aquella cuando la 1-{6-[(3-ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona (o su sal farmacéuticamente aceptable) se fórmula sola. Dosis apropiadas serán fácilmente apreciadas por aquellos con experiencia en la técnica.

Los siguientes ejemplos ilustran la invención pero no la limitan de alguna manera.

EJEMPLOS

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EJEMPLO 1

Preparación de tabletas redondas que contienen 0.05 mg de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona

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Los componentes del núcleo se pasan a través de un tamiz malla nominal 30 y después se mezclan juntos en un mezclador adecuado y se comprimen en una prensa de tabletas rotatoria para producir tabletas

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bicóncavas redondas con un diámetro de 9.525 mm y una profundidad de aproximadamente 0.8 mm a través de ambos lados de la tableta. La compresión se sigue mediante la desempolvado y verificación del metal. Las tabletas se transfieren a una bandeja de recubrimiento y se recubre a una ganancia objetivo de 4% (p/p).

La composición de las tabletas portadoras se proporciona posteriormente:

Núcleo

Componente	Peso (mg)
Celulosa microcristalina (Avicel PH-102)	210
Almidón pregelatinizado (Almidón 1500)	21
Estearato de magnesio	2.3
Total	233.3

Cubierta de película

Componente	Peso (mg)
Opadry blanco YS-1-7003	9.3
Agua purificada	c.s.*
Total	242.6

* removida durante el procesamiento

Solución portadora se prepara al disolver 4 g de hidroxipropil celulosa (Grado EF; HPC), 2 g de ácido cítrico anhidro y 0.02 g de hidroxianisol butilado (BHA) en metanol, filtrando a través de un filtro de 10 micras y después llevando el volumen final a 100 ml con metanol.

53

1-{6-[(3-Ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona se disuelve en la solución portadora con un sonicador hasta que se obtiene una solución uniforme con una concentración final de 5 mg/g (p/p).

5 Se dispensan 10 mg de la solución de dosificación en cada tableta en un arreglo de tabletas portadoras. Las tabletas se secan en un horno de aire forzado a ~40°C durante 10-20 minutos.

Composición de las tabletas finales es como sigue:

10

Componente	Peso (mg)
1-{6-[(3-Ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona	0.05
Portador (HPC al 4%/ácido cítrico al 2%/BHA al 0.02% en metanol*)	0.6
Tableta portadora	242.6
Total	243.3

* removido durante el procedimiento de fabricación

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EJEMPLOS 2-4

Preparación de tabletas redondas que contienen 0.002 mg, 0.01 mg o 0.2 mg de 1-{6-[(3-Ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona

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Las tabletas que contienen 0.002 mg, 0.01 mg o 0.2 mg de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona se preparan en la manera descrita en el ejemplo 1 excepto que la

concentración de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona en la solución de dosificación varía.

EJEMPLO 5

5 **Preparación de tabletas ovaladas que contienen 1 mg de 1-{6-[(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona**

Los componentes del núcleo se pasan a través de un tamiz malla
10 30 nominal y después se mezclan juntos en un mezclador adecuado y se comprimen en una prensa de tableta rotatoria para producir tabletas bicóncavas ovaladas con dimensiones de 15.9 mm x 8 mm x 3.4 mm con aproximadamente 0.9 mm a través de ambos lados. La compresión se sigue por desempolvado y verificación del metal. Las tabletas se transfieren a una
15 bandeja de recubrimiento y se recubren con una ganancia objetivo de 4% (p/p).

La composición de las tabletas portadoras se proporciona posteriormente:

20 **Núcleo**

Componente	Peso (mg)
Celulosa microcristalina (Avicel PH-102)	286.2
Almidón pregelatinizado (Almidón 1500)	28.6
Estearato de magnesio	3.2
Total	318.0

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Cubierta de película

Componente	Peso (mg)
Opadry blanco 00F18484	12.7
Agua purificada	c.s.*
Total	330.7

* removida durante el procesamiento

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Solución portadora se prepara al disolver 4 g de hidroxipropil celulosa (Grado EF; HPC), 2 g de ácido cítrico anhidro y 0.02 g de hidroxianisol butilado (BHA) en metanol, filtrando a través de un filtro de 10 micras y después llevando el volumen final a 100 ml con metanol.

10

1-{6-[(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona se disuelve en la solución portadora con un sonicador hasta que se obtiene una solución uniforme con una concentración final de 35 mg/g (p/p).

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Se dispensan 28.5 mg de la solución de dosificación en cada tableta en un arreglo de tabletas portadoras. Las tabletas se secan en un horno de aire forzado a ~50°C durante 10-20 minutos. Si es necesario o deseable, la temperatura de secado se puede elevar a, por ejemplo ~60°C y/o la duración de secado se puede incrementar a fin de asegurar la evaporación adecuada del solvente.

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* removido durante el procedimiento de fabricación

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Los componentes del núcleo se pasan a través de un tamiz malla 30 nominal y después se mezclan juntos en un mezclador adecuado y se comprimen en una prensa de tableta rotatoria para producir tabletas bicóncavas redondas con un diámetro de 7.9 mm y una profundidad de aproximadamente 0.8 mm a través de ambos lados de la tableta. La compresión se sigue por desempolvado y verificación del metal. Las tabletas se transfieren a una bandeja de recubrimiento y se recubren hasta una ganancia objetivo de 4% (p/p).

5d

La composición de las tabletas portadoras se proporciona posteriormente:

Núcleo

5	<table><tr><th>Componente</th><th>Peso (mg)</th></tr><tr><td>Celulosa microcristalina (Avicel PH-102)</td><td>162</td></tr><tr><td>Almidón pregelatinizado (Almidón 1500)</td><td>16.2</td></tr><tr><td>Estearato de magnesio</td><td>1.8</td></tr><tr><td>Total</td><td>180</td></tr></table>	Componente	Peso (mg)	Celulosa microcristalina (Avicel PH-102)	162	Almidón pregelatinizado (Almidón 1500)	16.2	Estearato de magnesio	1.8	Total	180
Componente	Peso (mg)										
Celulosa microcristalina (Avicel PH-102)	162										
Almidón pregelatinizado (Almidón 1500)	16.2										
Estearato de magnesio	1.8										
Total	180										

Cubierta de película

10	<table><tr><th>Componente</th><th>Peso (mg)</th></tr><tr><td>Opadry blanco 00F18484</td><td>7.2</td></tr><tr><td>Agua purificada</td><td>c.s.*</td></tr><tr><td>Total</td><td>187.2</td></tr></table>	Componente	Peso (mg)	Opadry blanco 00F18484	7.2	Agua purificada	c.s.*	Total	187.2
Componente	Peso (mg)								
Opadry blanco 00F18484	7.2								
Agua purificada	c.s.*								
Total	187.2								

* removida durante el procesamiento

Solución portadora se prepara al disolver 5 g de hidroxipropil
15 celulosa (Grado EF; HPC), 3 g de ácido cítrico anhidro en metanol, filtrando a
través de un filtro de 10 micras y después llevando el volumen final a 100 ml
con metanol.

1-{6-[(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-
piridinil}-2-pirrolidinona se disuelve en la solución portadora con un sonicador
20 (y también al usar un agitador magnético) hasta que se obtiene una solución
uniforme con una concentración final de 12.5 mg/g (p/p).

Se dispensan 4 mg de la solución portadora en cada tableta en
un arreglo de tabletas portadoras. Las tabletas se secan en un horno de aire

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forzado a ~50°C durante 10-20 minutos.

La composición de las tabletas finales es como sigue:

	Componente	Peso (mg)
	1-{6-[(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona	0.01
	Portador (HPC al 5%/ácido cítrico al 3% en metanol*)	0.4
5	Tableta portadora	187.2
	Total	187.6

* removido durante el procedimiento de fabricación

EJEMPLOS 7-11

10 **Preparación de tabletas redondas que contienen 0.002 mg, 0.005 mg, 0.02 mg, 0.05 mg o 0.1 mg de 1-{6-[(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona**

Las tabletas que contienen 0.002 mg, 0.005 mg, 0.02 mg, 0.05
15 mg o 0.1 mg de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona se preparan en la manera descrita en el ejemplo 6 excepto que la concentración de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona en la solución portadora varía.

Los siguientes ejemplos (ejemplo 12 y ejemplo 13) son
20 representativos de una tableta de ejemplo que se puede preparar de acuerdo con la invención.

61

EJEMPLO 12

Preparación de un sustrato portador de tableta de desintegración oralmente (ODT)

5 **a) Preparación de sustrato portador de ODT**

StarLac y Neotame se pasan a través de un tamiz de malla 20 nominal. La mezcla y el saborizante de menta no tamizado se transfieren a un mezclador adecuado y se mezcla por aproximadamente 10 minutos. Estearato de magnesio se pasa a través de un tamiz de malla 30 nominal, se transfiere al mezclador y la mezcla entera se mezcla por aproximadamente 2 minutos. Los pesos del material usado se calculan a partir de los porcentajes de peso proporcionados en el cuadro A. La mezcla se comprime hasta lograr las especificaciones adecuadas (por ejemplo tabletas redondas, cóncavas, intervalo de diámetro de ~8 mm a ~9.5 mm) en una prensa rotatoria adecuada utilizando maquinado de tableta apropiado. Las tabletas se pasan a través de un aparato para quitar el polvo y verificador de metal.

CUADRO A

20	Composición	Especificación	% (p/p)	Función
	StarLac*	Sin compendio	98.5%	Diluyente
	Saborizante de menta	Sin compendio	0.9%	Saborizante
	Neotame	NF	0.1%	Edulcorante
	Estearato de magnesio	Ph Eur/USP-NF/JP	0.5%	Lubricante

62

* StarLac: mezcla de 85% de monohidrato de alfa-lactosa (Ph. Eur/USP-NF) y 15% de almidón de maíz (Ph. Eur/USP-NF).

b) Preparación de cubierta de etilcelulosa para la aplicación a la

5 tableta mediante dispositivo de impresión indirecta de huecograbado

Se disuelve etilcelulosa en metanol con agitación, y se añade citrato de trietilo. Los pesos del material usado se calculan a partir de los pesos en porcentaje dados en el cuadro B. Se añade metanol suficiente para llevar al objetivo en base p/p. La solución se transfiere a la copa de tinta de

10 una máquina de impresión indirecta de huecograbado equipada con un negativo de imagen adecuado con una imagen redonda, diámetro ligeramente más pequeño que el diámetro de tableta real. Una almohadilla de polímero adecuada se instala para equilibrar la placa de imagen negativa. Las tabletas son presentadas al dispositivo de impresión indirecta de huecograbado en un

15 arreglo definido, equilibrando el negativo. El dispositivo de impresión indirecta de huecograbado puede aplicar 2-4 acuñaciones a la tableta portadora para aplicar una cubierta que proveerá una capa protectora para mitigar la infiltración del solvente en un sustrato portador no recubierto durante el procedimiento de dispensación de líquido.



CUADRO B

Composición	Especificación	% (p/p)	Función
Etilcelulosa	NF	30	Cubierta de barrera protectora
Citrato de trietilo	Ph. Eur./USP-NF	1.67	Plastificante
Metanol	Ph. Eur./USP-NF	c.s.*** a 100	Vehículo

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***Metanol eliminado mediante evaporación

EJEMPLO 13

Preparación alternativa de un sustrato portador de tableta de desintegración oralmente (ODT)

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Manitol, crospovidona XL, xilitol y Neotame se pasan a través de un tamiz de malla 20 nominal, la mezcla y el saborizante de menta no tamizado se transfieren a un mezclador adecuado y se mezcla adecuadamente por aproximadamente 10 minutos. Estearato de magnesio y dióxido de silicio coloidal se pasan a través de un tamiz de malla 30 nominal, se transfiere al mezclador y la mezcla completa se mezcla por aproximadamente 2 minutos. Los pesos del material usado se calculan a partir de pesos en porcentajes dados en el cuadro C. La mezcla se comprime para lograr las especificaciones deseadas (por ejemplo, tabletas redondas, bicóncavas, intervalo en diámetro de ~8 mm a ~9.5 mm) en una prensa rotatoria adecuada utilizando un maquinado de tableta apropiado. Las tabletas se pasan a través de un aparato para quitar el polvo y verificador de metal.

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CUADRO C

	Composición	Especificación	% (p/p)	Función
	Manitol (Grado 300 compresión directa)	Ph. Eur/USP-NF/JP	73.15%	Diluyente/edulcorante
5	Crospovidona XL	Ph. Eur/USP-NF	20.00%	Desintegrante
	Xilitol (Grado 300 para compresión directa)	Ph. Eur/USP-NF/JP	5.00%	Diluyente/edulcorante
	Saborizante de menta	Sin compendio	0.90%	Saborizante
	Neotame	NF	0.10%	Edulcorante
	Estearato de magnesio	Ph. Eur/USP-NF/JP	0.75%	Lubricante
10	Dióxido de silicio coloidal	Ph. Eur/USP-NF/JP	0.10%	Lubricante

Propiedades

La estabilidad de la sustancia de fármaco en las tabletas se puede probar como se expone posteriormente:

Se disuelven 5 tabletas en diluyente (1:9 acetonitrilo: 50 mm de ortofosfato dihidrógeno de potasio, se ajusta el pH a 3 con ácido ortofosfórico) para producir una concentración final de agente activo de entre 1-10 µg/ml y se sonica durante 10 minutos. Se verifica para completar la desintegración y se sonica adicionalmente si se requiere. Se deja enfriar a temperatura ambiente y después se centrifuga una alícuota de la muestra a 14,000 rpm. Se preparan muestras usando tabletas de placebo para actuar como muestras de control.



Usando las siguientes condiciones de instrumentos, se equilibra el sistema cromatográfico con 95% de A, 5% de B. Se registran los cromatogramas para la muestra y preparaciones de placebo.

Columna: XBridge C18 3 µm 15 cm x 4.6 mm i.d.

5 Temperatura de columna: 40°C

Fase móvil A: 10 mM de bicarbonato de amonio, pH 10 con amoniaco

Fase móvil B: acetonitrilo

Velocidad de flujo: 1 ml/min

10 Longitud de onda del detector: 250 nm

Volumen de inyección: 100 µl

Perfil de gradiente:

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Tiempo (min)	% A	% B
0	95	5
5	95	5
30	30	70
30.1	95	5

Siguiendo la comparación de los cromatogramas para identificar impurezas/productos de degradación, el contenido en porcentaje de cada impureza/producto de degradación en inyecciones de control y muestra se pueden calcular al dividir el área del pico de impureza/producto de degradación por el total sumado del pico para 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidona y todas las

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impurezas/productos de degradación, y multiplicando por 100.

El contenido de impureza total/producto de degradación se puede calcular al sumar el contenido en porcentaje de cada impureza/producto de degradación presente. Usualmente, solamente

5 impurezas/productos de degradación presentes en una cantidad mayor o igual a 0.05 o 0.03% se incluyen en el cálculo del contenido de impureza/producto de degradación.

NOVEDAD DE LA INVENCION

REIVINDICACIONES

5 1.- Una forma de dosificación que comprende: a) 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable; b) un estabilizador, que reduce la degradación de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona en la forma de dosificación cuando se compara con
10 una forma de dosificación que carece de dicho estabilizador; y c) un excipiente farmacéuticamente aceptable.

 2.- La forma de dosificación de conformidad con la reivindicación 1, caracterizada además porque comprende una tableta portadora, cuya tableta portadora es al menos parcialmente cubierta por una película que
15 comprende: a) 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable, y b) un estabilizador que reduce la degradación de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona en la forma de dosificación, cuando se compara con una forma de dosificación que carece de
20 dicho estabilizador.

 3.- La forma de dosificación de conformidad con la reivindicación 1 o reivindicación 2, caracterizada además porque contiene entre 1 µg y 1 mg de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-

pirrolidinona, cuando se mide como la cantidad de base libre presente.

4.- La forma de dosificación de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque comprende 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-

5 pirrolidinona, como una base libre.

5.- La forma de dosificación de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque dicho estabilizador se selecciona del grupo que consiste de ácido cítrico, ácido málico, ácido ascórbico, y sus sales, bicarbonato de sodio, hidroxianisol
10 butilado e hidroxitolueno butilado.

6.- La forma de dosificación de conformidad con la reivindicación 2, caracterizada además porque dicho estabilizador es ácido cítrico, y en donde la relación molar de la base libre a ácido cítrico está en el intervalo de 1.5:1 a 1:500.

15 7.- La forma de dosificación de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque dicha tableta portadora tiene al menos un hueco.

8.- La forma de dosificación de conformidad con la reivindicación 7, caracterizada además porque dicha película está presente en un hueco en
20 dicha tableta portadora.

9.- La forma de dosificación de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque sustancialmente no existe absorción de la 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-

69

benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable por la tableta portadora.

10.- La forma de dosificación de conformidad con la reivindicación 9, caracterizada además porque dicha tableta portadora está
5 recubierta.

11.- La forma de dosificación de conformidad con cualquiera de las reivindicaciones anteriores, caracterizada además porque dicha forma de dosificación está recubierta adicionalmente.

12.- Una forma de dosificación sustancialmente como se
10 describe en los ejemplos.

13.- Una forma de dosificación como se describe en los ejemplos 1-11.

14.- Un método de producción de una forma de dosificación como se define en la reivindicación 2, que comprende la dispensación de una
15 solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y un estabilizador sobre una tableta portadora.

15.- Un método de tratamiento de enfermedades neurológicas que comprende administrar a un hospedero en necesidad del mismo una
20 forma de dosificación como se define en cualquiera de las reivindicaciones 1 a 13.

16.- Uso de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente



aceptable en la elaboración de una forma de dosificación como se define en cualquiera de las reivindicaciones 1 a 13 para el tratamiento de enfermedades neurológicas.

17.- La forma de dosificación de conformidad con cualquiera de
5 las reivindicaciones 1 a 13 para usarse en el tratamiento de enfermedades neurológicas.

18.- Una solución o suspensión de 1-{6-[(3-ciclobutil-2,3,4,5-tetrahydro-1H-3-benzazepin-7-il)oxi]-3-piridinil}-2-pirrolidinona o su sal farmacéuticamente aceptable y un estabilizador en un sistema de solventes.

RESUMEN DE LA INVENCION

La presente invención se refiere a una forma de dosificación
novedosa, a un procedimiento para la preparación de la forma de dosificación
5 y al uso de la forma de dosificación en el tratamiento de trastornos
neurológicos y psiquiátricos.

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P09/1227F

PATENT COOPERATION TREATY

72

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: GLAXOSMITHKLINE Attn: Thornley, Rachel Corporate Intellectual Property (CN9251) 980 Great West Road Brentford, Middlesex TW8 9GS GRANDE BRETAGNE		NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION	
21 MAY 2009 ATTN: APB Date of mailing (day/month/year) 25/05/2009 TB		(PCT Rule 44.1)	
Applicant's or agent's file reference MXG/PB62338		FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/EP2008/052430		International filing date (day/month/year) 28/02/2008	
Applicant GLAXO GROUP LIMITED			

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Saskia Stark
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 65.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MXG/PB62338	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2008/052430	International filing date (day/month/year) 28/02/2008	(Earliest) Priority Date (day/month/year) 01/03/2007
Applicant GLAXO GROUP LIMITED		

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

This international search report consists of a total of 6 sheets.

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

1. Basis of the report

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

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

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

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

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

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

4. With regard to the title,

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

5. With regard to the abstract,

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

6. With regard to the drawings,

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/052430

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K9/20 A61K9/50 A61K31/55

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/123723 A (GLAXO GROUP LTD [GB]; BAMFORD MARK JAMES [GB]; PICKERING PAULA LOUISE) 29 December 2005 (2005-12-29) page 1, lines 3-5 page 2, lines 12-14, 24-26 page 3, lines 6-18 page 6, lines 28-38 page 7, lines 1-28, 28-35 page 8, lines 10-28	1-11, 14-18
A	WO 2006/018260 A (GLAXO GROUP LTD [GB]; PARR CHRISTOPHER ALLAN [GB]; PICKERING PAULA LOU) 23 February 2006 (2006-02-23) the whole document ----- -/-	1-11, 14-18

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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

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

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

Z document member of the same patent family

Date of the actual completion of the international search

7 May 2009

Date of mailing of the international search report

25/05/2009

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2260 HV Rijswijk
Tel. (+31-70) 340-2040.
Fax: (+31-70) 340-3016

Authorized officer

Raposo, Antonio

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/052430

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/042491 A (ARENA PHARM INC [US]; SMITH BRIAN [US]; GILSON CHARLES III [US]; SCHUL) 12 May 2005 (2005-05-12) the whole document	1-11, 14-18
A	WO 2004/056369 A (GLAXO GROUP LTD [GB]; BAMFORD MARK JAMES [GB]; DEAN DAVID KENNETH [GB]) 8 July 2004 (2004-07-08) the whole document	1-11, 14-18

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 12,13

Claims 12 and 13 makes reference to the examples disclosed in the description. However, the claims must not, in respect of the technical features of the invention, rely on references to the description (Rule 6.2 PCT). Thus, no opinion will be formulated in terms of novelty, inventive step and industrial applicability for claims 12 and 13.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/052430

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 12, 13
because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/052430

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005123723 A	29-12-2005	AR 051919 A1	21-02-2007
		EP 1756094 A1	28-02-2007
		JP 2008502644 T	31-01-2008
		US 2007232590 A1	04-10-2007
WO 2006018260 A	23-02-2006	AR 050698 A1	15-11-2006
		EP 1778643 A1	02-05-2007
		JP 2008509955 T	03-04-2008
		US 2007208005 A1	06-09-2007
WO 2005042491 A	12-05-2005	US 2008009478 A1	10-01-2008
WO 2004056369 A	08-07-2004	AU 2003294909 A1	14-07-2004
		BR 0317483 A	16-11-2005
		CA 2509413 A1	08-07-2004
		EP 1572215 A1	14-09-2005
		IS 7941 A	18-07-2005
		JP 2006512412 T	13-04-2006
		KR 20050088195 A	02-09-2005
		KR 20070089762 A	31-08-2007
		MA 27582 A1	03-10-2005
		MX PA05006567 A	16-08-2005
		NZ 540148 A	30-11-2007
		US 2009105226 A1	23-04-2009
		US 2006040918 A1	23-02-2006
		US 2007299056 A1	27-12-2007

PATENT COOPERATION TREATY

8

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To: see form PCT/ISA/220	WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) 25/05/2008 <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px 5px;">Date of mailing (day/month/year)</td> <td style="padding: 2px 5px;">see form PCT/ISA/210 (second sheet)</td> </tr> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px 5px;">Applicant's or agent's file reference see form PCT/ISA/220 MXG/P862338</td> <td style="width: 50%; padding: 2px 5px;">FOR FURTHER ACTION See paragraph 2 below</td> </tr> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%; padding: 2px 5px;">International application No. PCT/EP2008/052430</td> <td style="width: 33%; padding: 2px 5px;">International filing date (day/month/year) 28.02.2008</td> <td style="width: 33%; padding: 2px 5px;">Priority date (day/month/year) 01.03.2007</td> </tr> </table> International Patent Classification (IPC) or both national classification and IPC INV. A61K9/00 A61K9/20 A61K9/50 A61K31/55 Applicant GLAXO GROUP LIMITED	Date of mailing (day/month/year)	see form PCT/ISA/210 (second sheet)	Applicant's or agent's file reference see form PCT/ISA/220 MXG/P862338	FOR FURTHER ACTION See paragraph 2 below	International application No. PCT/EP2008/052430	International filing date (day/month/year) 28.02.2008	Priority date (day/month/year) 01.03.2007
Date of mailing (day/month/year)	see form PCT/ISA/210 (second sheet)							
Applicant's or agent's file reference see form PCT/ISA/220 MXG/P862338	FOR FURTHER ACTION See paragraph 2 below							
International application No. PCT/EP2008/052430	International filing date (day/month/year) 28.02.2008	Priority date (day/month/year) 01.03.2007						

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

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

2. FURTHER ACTION

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

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

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

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA: European Patent Office D-80298 Munich Tel. +49 89 2399-0 Fax: +49 89 2399-4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Raposo, Antonio Telephone No. +49 89 2399-4743
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2008/052430

Box No. I Basis of the opinion

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

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2008/052430

23

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 12, 13

because:

☒ the said international application, or the said claims Nos. 12, 13 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☒ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2008/052430



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

1. Statement

Novelty (N)	Yes: Claims	<u>1-11,14-18</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-11,14-18</u>
Industrial applicability (IA)	Yes: Claims	<u>1-11,14-18</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

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

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2008/052430



Re Item III

1. Claims 12 and 13 makes reference to the examples disclosed in the description. However, the claims must not, in respect of the technical features of the invention, rely on references to the description (Rule 6.2 PCT). Thus, no opinion will be formulated in terms of novelty, inventive step and industrial applicability for claims 12 and 13.

Re Item V

1. Reference is made to the following documents:

D1: WO2005123723

2. The patentability of claims 15 and 16 is inter alia dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT. Their assessment will be carried out based on the alleged effects of the compositions searched in the International Search Report.

3. Novelty

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-11 and 14-18 is new in the sense of Article 33(2) PCT.

4. Inventive Step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-11 and 14-18 does not involve an inventive step in the sense of Article 33(3) PCT.

4.1 For claim 1:

4.1.1 The closest prior art is considered to be D1. D1 teaches the use of a composition comprising a histamine H3 antagonist such as 1-{6-[(3-cyclopentyl)-2,3,4,5-tetrahydro-1



H-3-benzazepin-7-yl)oxy]-3-pyridinyl]-2-pyrrolidinone or a pharmaceutically acceptable salt thereof and pharmaceutical excipients for the treatment of neurological and psychiatric disorders such as Alzheimer's disease (page 1, lines 3-5; page 2, lines 12-14, 24-26; page 3, lines 6-18; page 6, lines 28-38; page 7, lines 1-13, 28-35; page 8, lines 10-28). The difference in claim 1 is that the histamine H3 antagonist is specifically 1-{6-[(3-cyclopentyl-2,3,4,5-tetrahydro-1-H-3-benzazepin-7-yl)oxy]-3-pyridinyl]-2-pyrrolidinone or a pharmaceutically acceptable salt thereof. The technical effect provided by this difference is the alternative formulation. Thus, the problem to be solved is to provide an alternative formulation comprising a histamine H3 antagonist.

4.1.2 It would be obvious to the person skilled in the art, namely when the same result is to be achieved, to apply these features presented in D1 to a specific histamine H3 antagonist such 1-{6-[(3-cyclopentyl-2,3,4,5-tetrahydro-1-H-3-benzazepin-7-yl)oxy]-3-pyridinyl]-2-pyrrolidinone or a pharmaceutically acceptable salt thereof.

4.2 The reasoning applied for claim 1, also applies the subject matter of claims 14-18.

4.3 Dependent claims 2-11 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step.

5. Industrial Applicability

5.1 Claims 1-11 and 14-18 are considered to be industrially applicable in the sense of Article 33(4) PCT.

Re Item VIII

1. The term **substantially** (in claim 9) is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 September 2008 (04.09.2008)

PCT

(10) International Publication Number
WO 2008/104590 A3

(51) International Patent Classification:

A61K 9/00 (2006.01) A61K 9/50 (2006.01)
A61K 9/20 (2006.01) A61K 31/55 (2006.01)

(21) International Application Number:

PCT/EP2008/052430

(22) International Filing Date:

28 February 2008 (28.02.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/892,267 1 March 2007 (01.03.2007) US

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CLARKE, Alan James [US/US]; GlaxoSmithKline, 1250 South Collegeville Road, P.O. Box 5089, Collegeville, Pennsylvania 19426 (US). CULLINGFORD, David Geoffrey [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). LI, Yu [CN/US]; GlaxoSmithKline, 1250 South Collegeville Road, P.O. Box 5089, Collegeville, Pennsylvania 19426 (US).

(74) Agents: THORNLEY, Rachel et al.; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available):

ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

2 July 2009

WO 2008/104590 A3

(54) Title: NOVEL DOSAGE FORM

(57) Abstract: The present invention relates to a novel dosage form, to a process for preparing the dosage form and to the use of the dosage form in the treatment of neurological and psychiatric disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/052430

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K9/20 A61K9/50 A61K31/55

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/123723 A (GLAXO GROUP LTD [GB]; BAMFORD MARK JAMES [GB]; PICKERING PAULA LOUISE) 29 December 2005 (2005-12-29) page 1, lines 3-5 page 2, lines 12-14, 24-26 page 3, lines 6-18 page 6, lines 28-38 page 7, lines 1-28, 28-35 page 8, lines 10-28	1-11, 14-18
A	WO 2006/018260 A (GLAXO GROUP LTD [GB]; PARR CHRISTOPHER ALLAN [GB]; PICKERING PAULA LOU) 23 February 2006 (2006-02-23) the whole document	1-11, 14-18

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

E earlier document but published on or after the international filing date

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

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

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

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

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

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

A document member of the same patent family

Date of the actual completion of the international search

7 May 2009

Date of mailing of the international search report

25/05/2009

Name and mailing address of the ISA/

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

Authorized officer

Raposo, Antonio

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/052430

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/042491 A (ARENA PHARM INC [US]; SMITH BRIAN [US]; GILSON CHARLES III [US]; SCHUL) 12 May 2005 (2005-05-12) the whole document -----	1-11, 14-18
A	WO 2004/056369 A (GLAXO GROUP LTD [GB]; BAMFORD MARK JAMES [GB]; DEAN DAVID KENNETH [GB]) 8 July 2004 (2004-07-08) the whole document -----	1-11, 14-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/052430

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 12, 13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 12,13

Claims 12 and 13 makes reference to the examples disclosed in the description. However, the claims must not, in respect of the technical features of the invention, rely on references to the description (Rule 6.2 PCT). Thus, no opinion will be formulated in terms of novelty, inventive step and industrial applicability for claims 12 and 13.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/052430

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005123723 A	29-12-2005	AR 051919 A1 EP 1756094 A1 JP 2008502644 T US 2007232590 A1	21-02-2007 28-02-2007 31-01-2008 04-10-2007
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No. 09-097361- -00000-0000

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AREQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCION



MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente [✓]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- ◆ Descripción de la invención [✓]
- ◆ Dibujos de ser estos pertinentes [✓]
- ◆ Comprobante de pago de las tasas establecidas [✓]

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Eduar Navarro

Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5,7y10
Conmutador: 3 82 0840
Fax: 3505220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá D.C. - Colombia