PTO-1390 (Rev. 09-2007)updated 10/04/07 by IPDAS/BSKB
Approved for use through 03/31/2007. OMB 0651-0021
U. S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
0020-5610PUS1	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
11/791,678 NEW	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP2006/310571	26 May 2006	26 May 2005

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITION

APPLICANT(S) FOR DO/EO/US
Kazuyuki FUJIHARA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
3. [x] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected (Article 31).
5. [x] A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [x] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [x] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [x] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [x] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [x] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [x] A preliminary amendment.
14. [ ] An Application Data Sheet under 37 CFR 1.76.
15. [ ] A substitute specification.
16. [ ] A power of attorney and/or change of address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 – 1.825.
18. [ ] A second copy of the published International Application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).

Birch, Stewart, Kolasch & Birch, LLP

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
11/919678 NEW	PCT/JP2006/310571	0020-5610PUS1

20. [x] Other items or information: Return Receipt Postcard; PCT/IB/308 (2 sheets); PCT/IB/304; PCT/ISA/237 (4 sheets); PCT/ISA/210; Drawings (3 sheets)

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. [x] Basic national fee (37 CFR 1.492(a)) $310	$ 310.00	
22. [x] Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4).....$0 All other situations $210	$ 210.00	
23. [x] Search fee (37 CFR 1.492(b)) If the written opinion of the ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) .....$0 Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority .....$100 International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB.....$410 All other situations.....$510	$ 410.00	
TOTAL OF 21, 22 and 23 =	$ 930.00	

[ ] Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) or in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)).
The fee is **$260** for each additional 50 sheets of paper or fraction thereof.

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE	
57 - 100 =	/50 =		x $260.00	$

Surcharge of **$130** for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)). $

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	24 - 20 =	4	x $50	200.00
Independent claims	5 - 3 =	2	x $210	420.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $370	
			TOTAL OF ABOVE CALCULATIONS =	$ 1,550.00

[ ] Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.

SUBTOTAL = $ 1,550.00

Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). $

TOTAL NATIONAL FEE = $ 1,550.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property + $ 40.00

$

TOTAL FEES ENCLOSED = $

Amount to be refunded: $

Amount to be charged $ **1,590.00**

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IAP17 Rec'd PCT/PTO 31 OCT 2007

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [x] Please charge my Deposit Account No. 02-2448 in the amount of $ 1,590.00 to cover the above fees.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448 .

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended paying fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

SEND ALL CORRESPONDENCE TO:

#32,868
SIGNATURE

for Mark J. Nuell
NAME

CUSTOMER NUMBER: 02292

36,623
REGISTRATION NUMBER

October 31, 2007
/scp

PTO-1390 (Rev. 09-2007)updated 10/04/07 by IPDAS/BSKB
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 0020-5610PUS1

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 11791678 NEW

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP2006/310571	26 May 2006	26 May 2005

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITION

APPLICANT(S) FOR DO/EO/US
Kazuyuki FUJIHARA

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SEND ALL CORRESPONDENCE TO:

#32,868
SIGNATURE

for Mark J. Nuell
NAME

CUSTOMER NUMBER: 02292

36,623
REGISTRATION NUMBER

October 31, 2007
/scp

Docket No.: 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

International Application No.: PCT/JP2006/310571

Application No.: NEW | Art Unit: N/A

Filed: October 31, 2007 | Examiner: Not Yet Assigned

For: PHARMACEUTICAL COMPOSITION

PRELIMINARY AMENDMENT

MS PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INTRODUCTORY COMMENTS

The following preliminary amendments and remarks are respectfully submitted in connection with the above-identified application.

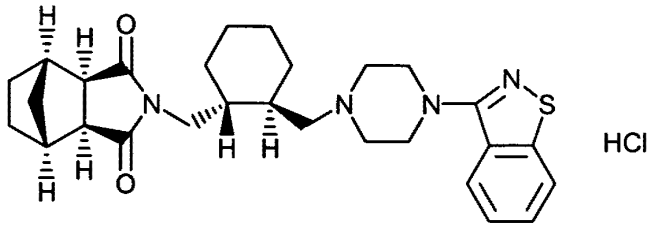
This amendment includes:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

1. (Original) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder.

2. (Original) An oral preparation which is prepared by granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

3. (Original) An oral preparation which is prepared by granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder.

4. (Currently Amended) The oral preparation of ~~any one of claims 1 to 3~~claim 1 wherein the water-soluble excipient is mannitol or lactose.

5. (Original) A method of granulation of a powder mixture which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

6. (Original) A method of granulation of a powder mixture which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by using a solution or dispersion of lurasidone and a water-soluble polymer binder.

7. (Original) The method of granulation of claim 5 wherein the water-soluble excipient is mannitol or lactose.

8. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

9. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt).

11. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

12. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the water-soluble excipient is mannitol or lactose and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

16. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

18. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

19. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

20. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein an average particle size of lurasidone is 0.1 to 8 μm. 23. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Currently Amended) The oral preparation of ~~any one of claims 1 to 4~~claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

REMARKS

The claims have been amended to remove the multiple dependencies listed therein. Claims 1-24 are pending in this application.

CONCLUSION

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: October 31, 2007

Respectfully submitted,

By #34,868
for Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant

Docket No.: 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

Application No.: NEW | Confirmation No.: N/A

Filed: October 31, 2007 | Art Unit: N/A

For: PHARMACEUTICAL COMPOSITION | Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

MS PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement accompanies the new patent application submitted herewith.

A summary/abstract translation of the non-English language references BA and BB is enclosed. Reference AA corresponds to reference BA. The references can be found cited in the International Search Report.

A concise explanation of relevance of the items listed on form PTO/SB/08 is in the form of an English language copy of a Search Report from a foreign patent office, issued in a counterpart application, which refers to the relevant portions of the references.

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: October 31, 2007

Respectfully submitted,

By #32,868
Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant

Attachment(s)

11/919678

IAP05Rec'd PCT 31 OCT 2007

Used in Lieu of PTO/SB/08A/B
(Based on PTO 10-07 version)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	NEW
				Filing Date	October 31, 2007
				First Named Inventor	Kazuyuki FUJIHARA
(Use as many sheets as necessary)				Art Unit	N/A
				Examiner Name	Not Yet Assigned
Sheet	1	of	1	Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-2004/0028741-A1	02-12-2004	Fujihara	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO-02/24166-A1	03-28-2002			ABS
	BB	WO-2004/078173-A1	09-16-2004			ABS
	BC	JP-8-325146-A	12-10-1996			

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Birch, Stewart, Kolasch & Birch, LLP

DRN//scp

DESCRIPTION

PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

[0001]

The present invention relates to an oral preparation with a good disintegration which comprises as an active ingredient N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone). More particularly, the present invention relates to a preparation for oral administration, particularly a tablet, comprising lurasidone as an active ingredient, which has an equivalent dissolution profile of the active ingredient even though contents of the active ingredient therein are varied.

BACKGROUND ART

[0002]

Patent Document 1 discloses that a compound such as lurasidone can be orally administered and an oral preparation can be prepared by blending an active ingredient with a conventional carrier, excipient, binder, stabilizer and the like, but there is no disclosure of an oral preparation which shows a rapid dissolution and has an equivalent dissolution profile of the active ingredient even though contents of the active ingredient therein are varied in the wide range, particularly an oral preparation with increased contents of the active ingredient which has a similar dissolution profile to that of multiple tablets with a lower content of the active ingredient per tablet.

[0003]

For the purpose of securing the bioequivalence when

pharmaceutical preparations with different contents of the active ingredient were administered so as to be the same dose to each other, a guideline has been issued, i.e., "Guideline for Bioequivalence Studies of Oral Solid Dosage Forms with Different Content" (Notification No. 64 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, promulgated on February 14, 2000) by which it has been required that pharmaceutical preparations with different contents should have an equivalent dissolution profile in each test solution such as buffers of pH1.2, 3.0 to 5.0 and 6.8 (which correspond to the pH values of stomach, intestine and oral cavity, respectively), water, and saline.

[0004]

Patent Document 2 discloses an oral preparation comprising lurasidone as an active ingredient, which shows a rapid dissolution and has an equivalent dissolution profile even though contents of the active ingredient therein are varied, particularly an oral preparation with increased contents of the active ingredient which has an equivalent dissolution profile to that of multiple tablets with a lower content of the active ingredient per tablet and can release a slightly water-soluble active ingredient therefrom at a desired concentration.

[0005]

Patent Document 2 further discloses an oral preparation, particularly a tablet, which shows a rapid dissolution of the active ingredient even though contents of the active ingredient therein are varied in the range of several mg to several tens of mg (e.g. in the range of 5 mg to 20 mg or in the range of 5 mg to 40 mg), and further has an equivalent dissolution profile in the same componential ratio. An oral preparation has been frequently required to be a preparation with higher contents of the active ingredient in order to get higher clinical effects, or a preparation which has an equivalent dissolution profile to

that of multiple tablets and can release the active ingredient therefrom at a desired concentration in wider ranges of contents in order to adjust clinical effects depending on conditions of patients. The art disclosed in Patent Document 2 may provide an oral preparation which has an equivalent dissolution profile in the range of 5 mg to 40 mg of lurasidone per tablet, as shown in Figure 1. However, as shown in Figure 2, when the content of the active ingredient per tablet was increased to double, i.e., 80 mg tablet, it could not have an equivalent dissolution profile. Hence, it remains in a state of administering multiple tablets at one time or using a tablet having a big size which is difficult to administer. Therefore, for such a slightly water-soluble active ingredient as lurasidone, it has been difficult to provide an oral preparation having an equivalent dissolution profile even in high content or in wider ranges of contents of the active ingredient.

[0006]

In Patent Document 2, a water-soluble polymer binder includes starch, but there is no description about a pregelatinized starch therein. The pregelatinized starch is known to remarkably improve a disintegration and a dissolution of a pharmaceutical composition as described, for example, in Patent Document 3, but it is often used, typically, in 10% or less of contents as also described in Non-patent Document 1.

[0007]

Patent Document 1: JP2800953

Patent Document 2: WO2002/024166

Patent Document 3: JP2000-26292

Non-patent Document 1: Handbook of Pharmaceutical Excipients, 2nd edition, 491, 1994, The Pharmaceutical Press

DISCLOSURE OF INVENTION

PROBLEMS TO BE RESOLVED BY THE INVENTION

[0008]

The present invention is directed to provide an oral preparation comprising lurasidone as an active ingredient which shows a rapid dissolution and has an equivalent dissolution profile even though contents of the active ingredient therein are varied in the wide range, particularly an oral preparation with increased contents of the active ingredient which has a similar dissolution profile to that of multiple tablets with a lower content of the active ingredient per tablet and can release the active ingredient therefrom at a desired concentration.

[0009]

The present invention is directed to provide a preparation for oral administration which comprises as an active ingredient N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (hereinafter referred to as lurasidone), which has an equivalent dissolution profile of the active ingredient even though contents of the active ingredient therein are varied.

MEANS OF SOLVING THE PROBLEMS

[0010]

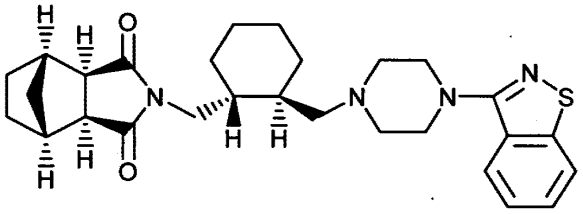
The present inventors have intensively studied in order to solve the above problems and found to solve said problems by means of the following methods.

[0011]

The present invention includes the following embodiments:

[0012]

(1) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder.

(2) An oral preparation which is prepared by granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

(3) An oral preparation which is prepared by granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder.

(4) The oral preparation of any one of (1) to (3) wherein the water-soluble excipient is mannitol or lactose.

(5) A method of granulation of a powder mixture which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

(6) A method of granulation of a powder mixture which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by using a solution or dispersion of lurasidone and a water-soluble polymer binder.

(7) The method of granulation of (5) wherein the water-soluble excipient is mannitol or lactose.

(8) The oral preparation of any one of (1) to (4) wherein the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

(9) The oral preparation of any one of (1) to (4) wherein the

pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

(10) The oral preparation of any one of (1) to (4) wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt).

(11) The oral preparation of any one of (1) to (4) wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

(12) The oral preparation of any one of (1) to (4) wherein a content of lurasidone per tablet is 10 to 160 mg.

(13) The oral preparation of any one of (1) to (4) wherein a content of lurasidone per tablet is 20 to 120 mg.

(14) The oral preparation of any one of (1) to (4) wherein a content of lurasidone per tablet is 40 to 120 mg.

(15) The oral preparation of any one of (1) to (4) wherein the water-soluble excipient is mannitol or lactose and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

(16) The oral preparation of any one of (1) to (4) wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

(17) The oral preparation of any one of (1) to (4) wherein the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

(18) The oral preparation of any one of (1) to (4) wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

(19) The oral preparation of any one of (1) to (4) wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is

incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

(20) The oral preparation of any one of (1) to (4) wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

(21) The oral preparation of any one of (1) to (4) wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

(22) The oral preparation of any one of (1) to (4) wherein an average particle size of lurasidone is 0.1 to 8 μm.

(23) The oral preparation of any one of (1) to (4) wherein the pregelatinized starch contains water soluble matter of 30% or less.

(24) The oral preparation of any one of (1) to (4) wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

EFFECTS OF INVENTION

[0013]

It has been confirmed in the art disclosed in Patent Document 2 that a pharmaceutical preparation with low contents of lurasidone up to 40 mg per tablet could provide an oral preparation having an equivalent dissolution profile. However, a pharmaceutical preparation with higher contents of lurasidone could not have an equivalent dissolution profile. Therefore, double amounts or more of the preparation with low contents should have been administered to a patient in need of high doses of lurasidone, which imposed increased burdens on the patient, and hence an improvement thereon has been required. The preparation of the present invention which comprises a pregelatinized starch can provide

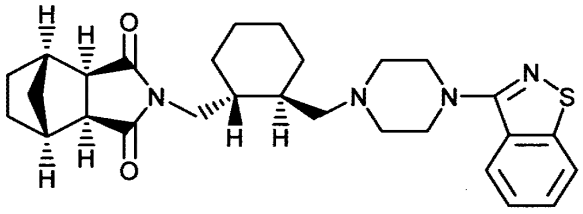
an oral preparation with higher contents of lurasidone which imposes less of burdens on a patient. Additionally, the present invention can provide an oral preparation with high contents of lurasidone, and a preparation for oral administration which has an equivalent dissolution profile even though contents of lurasidone therein are varied. Moreover, the preparations are excellent for a long-term conservation.

BEST MODE FOR CARRYING OUT THE INVENTION

[0014]

N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptane-dicarboxyimide hydrochloride (lurasidone) refers to a compound of the following formula:

[0015]



(1)

(see, for example, JP2800953). Lurasidone is known to exhibit a psychotropic effect, and it is useful as a therapeutic agent for schizophrenia, etc. Said compound is incorporated into the preparation, for example, in the range of 10 to 50% by weight, preferably in the range of 20 to 45% by weight, particularly in the range of 20 to 45% by weight on the basis of the total weight of a tablet. Additionally, the compound is preferably finely milled, for example, 90% by volume or more of particles have 27 μm or less of particle size, and average particle size in a volume ratio (i.e. 50% by volume particle size) includes, for example, in the range of 0.1 to 8 μm, preferably in the range of 1 to 4 μm. The contents of lurasidone are 10 to 160 mg, preferably 20 to

120 mg, more preferably 40 to 120 mg per tablet.

[0016]

The "pregelatinized starch" refers to those prepared by pregelatinizing various kinds of starch (e.g. corn starch, potato starch, wheat starch, rice starch, tapioca starch, etc.), and may include pregelatinized starch or partly pregelatinized starch described in Japanese Pharmaceutical Excipients. The pregelatinized starch has a pregelatinizing ratio, for example, in the range of 50 to 100%, preferably in the range of 50 to 95%, more preferably in the range of 80 to 95%. Additionally, the pregelatinized starch contains water soluble matter of, for example, 40% or less, more preferably 30% or less. Such a pregelatinized starch is typically used in a powder which average particle size is in the range of 1 to 1000 μm, preferably in the range of 1 to 500 μm, more preferably in the range of 10 to 100 μm. A commercially available pregelatinized starch suitable for the present invention includes, for example, partly pregelatinized starch such as PCS (brand name, manufactured by Asahi Kasei Corporation) or Starch 1500 (brand name, manufactured by Colorcon, Inc.), etc. Among the above pregelatinized starch, partly pregelatinized starch such as PCS (brand name, manufactured by Asahi Kasei Corporation) is preferably used. A pregelatinizing ratio of partly pregelatinized starch is preferably in the range of 50 to 95%, more preferably in the range of 80 to 95%. The pregelatinized starch used in the present invention is in the range of 10% to 50%, preferably in the range of 10% to 40%, particularly in the range of 20% to 30% by weight of the preparation.

[0017]

The "water-soluble excipient" includes, for example, mannitol, lactose, saccharose, sorbitol, D-sorbitol, erythritol, xylitol, etc. More preferable one includes mannitol and lactose. Further preferable one may include mannitol. Also, said water-soluble excipient may be used

alone, or two or more thereof may be used together. The water-soluble excipient is incorporated in an amount of, for example, the range of 30 to 80% by weight, preferably the range of 40 to 60% by weight on the basis of the total weight of a tablet. The average particle size of mannitol is, for example, in the range of 10 to 200 μm.

[0018]

The "water-soluble polymer binder" includes, for example, hydroxypropylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, etc. More preferable one includes hydroxypropylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone or polyvinyl alcohol. Said water-soluble polymer binder may be used alone, or two or more thereof may be used together. The water-soluble polymer binder is incorporated in an amount of, for example, the range of 0.5 to 10% by weight, preferably the range of 1 to 5% by weight on the basis of the total weight of a tablet.

The oral preparation in the form of a pharmaceutical composition of the present invention refers to a pharmaceutical preparation which is formulated into tablet, capsule, granule or fine granule. Said preparation may be formulated by a conventional method into tablet, capsule, granule or fine granule by using water-soluble excipient as well as water-insoluble excipient, binder, disintegrant, lubricant, etc. The following agents may be added thereto.

[0019]

The "water-insoluble excipient" includes, for example, corn starch, crystalline cellulose, etc. Said water-insoluble excipient may be used alone, or two or more thereof may be used together.

[0020]

The "disintegrant" includes, for example, corn starch, crystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium,

carboxymethyl starch sodium, crospovidone, etc. Said disintegrant may be used alone, or two or more thereof may be used together. The disintegrant is used in an amount of, for example, the range of 0 to 10% by weight, preferably the range of 0.5 to 5% by weight on the basis of the total weight of a tablet.

[0021]

The "lubricant" includes, for example, magnesium stearate, talc, polyethylene glycol, silica, hydrogenated vegetable oil, etc.

[0022]

The oral preparation of the present invention may be prepared according to a conventional method depending on a desired dosage form.

(1) Preparation of an aqueous solution of water-soluble polymer binder:

A water-soluble polymer binder is dissolved in purified water. The amount of the water-soluble polymer binder is, for example, in the range of 1 to 20% by weight, preferably in the range of 2 to 8% by weight of purified water.

(2) Preparation of granule comprising lurasidone:

To a fluid bed granulator are charged excipient including lurasidone, mannitol and partly pregelatinized starch, and disintegrant, and thereto is sprayed the water-soluble polymer binder prepared in the above process (1) to be granulated.

[0023]

The apparatus for granulation includes, for example, one classified into fluid bed granulation, high share granulation, roto fluid bed granulation, etc., but it is not limited thereto.

(3) Drying of granule:

The above-obtained granule is dried either under reduced pressure or atmospheric pressure. The drying is carried out so that the loss on dry measured by infrared moisture meter is, for example, within

3% by weight, preferably 1 to 2% by weight.

(4) Blending of lubricant:

To the granule dried in the above (3) is added lubricant to be mixed. For mixing, for example, a blending machine classified into diffusion mixers [Tumble] is used. Specifically, tumble blender, V blenders, double cone, bin tumble, etc. are used, but it is not limited thereto.

(5) Compression:

The above mixture is compressed to give a tablet.

[0024]

The apparatus for compression includes, for example, one classified into tablet press, etc. The compression hardness is selected, for example, from the range of 30 to 200N.

(6) Film-coating is optionally carried out:

The above-obtained tablet may be optionally subjected to film-coating, if necessary. The apparatus for coating includes, for example, one classified into a coating pan. Preferable one includes one classified by perforated coating system.

[0025]

The coating agent includes, for example, a mixture of base material (e.g. hydroxypropyl methylcellulose, hydropropylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, etc.) and plasticizer (e.g. polyethylene glycol, propylene glycol, triacetin, triethyl citrate, glycerin, glycerin fatty acid ester, polyethylene glycol, etc.). If necessary, an additive such as titanium oxide may be also added therein. After film-coating, carnauba wax, etc. may be also added as polishing agent therein.

(7) Drying:

The above-obtained tablet is dried. The drying is carried out either under reduced pressure or atmospheric pressure so that the loss

on dry measured by infrared moisture meter is, for example, within 3% by weight, preferably 1 to 2% by weight.

[0026]

Examples of the present invention are illustrated below. Said examples are intended to exemplify the present invention but not to limit the present invention thereto.

EXAMPLES

Example 1

[0027]

A. A film-coated tablet comprising 80 mg of lurasidone (Example 1)

Granules, uncoated tablets and FC tablets comprising the following components are sequentially prepared. The charging amounts shown in parentheses in the following description are an example for preparing the formulation shown in Example 1.

According to the preparation method, other examples may be also prepared in principle, provided that the charging amounts are needed to be changed depending on formulations.

[0028]

B. Preparation method

(1) Preparation of binding solution (5% aqueous hydroxypropyl methylcellulose solution):

Hydroxypropyl methylcellulose (32 g) as water-soluble polymer binder was dissolved in purified water (608 g) to give binding solution.

(2) Granulation:

Lurasidone (320 g), mannitol (576 g), partly pregelatinized starch (320 g) and croscarmellose sodium (16 g) were charged to a fluid bed granulator (Multiplex MP-01/manufactured by Powrex Corporation), and the mixture was granulated by spray granulation under the following conditions using the binding solution prepared in the above (1)

to give granule powder. To the obtained granule powder was added magnesium stearate to give a granule for compression having a formulation (b) after mixing (40 rpm, 5 minutes). Magnesium stearate was mixed in amounts calculated from a formulation on the basis of yields of granule powder.

Conditions for granulation

Temperature for supplying air: 60°C

Airflow: 50 to 65 m^3 /hr

Spray speed: 13 g/min

Diameter of spray nozzle: 1.2 mm

Spray pressure: 0.12MPa

Gun position: the middle stand

(3) Compression:

The granule for compression prepared in the above (2) was compressed by HT-AP12SS-II (manufactured by Hata Iron Works Co., Ltd.) to give a tablet.

Pestle size: φ10 mm 14R

Thickness: 4.20 to 4.30 mm

Compression pressure: 10 KN

(4) Coating:

The uncoated tablet prepared in the above (3) were coated by using High Coater HCT30N (manufactured by Freund Industrial Co., Ltd.) under the following conditions so as to control amounts of the coat to 5 mg, and thereto was added carnauba wax after coating to give a film-coated tablet.

FC conditions

Temperature for supplying air: 80°C

Airflow: 0.6 m^3 /min

Rotation rate of pan: 25 rpm

Spray pressure: 0.15MPa

Liquid flow rate: 5 g/min

The preparation obtained in the above method was evaluated a quality thereof according to the following methods, and the present invention has been achieved on the basis of the knowledge obtained therein.

[0029]

C. Quality evaluation

(1) Dissolution test

A manufactured preparation was subjected to the dissolution test according to the Japanese Pharmacopoeia, Dissolution test, Method 2. Measuring conditions are shown below.

Test solution: Diluted McIlvaine buffer, pH4.0

Rotation rate of paddle: 50 rpm

Test fluid: 900 ml

(2) Similarity of dissolution profiles

A similarity factor f2 shown in Scale-Up and Past-Approval Changes for Intermediate Release Products (SUPAC-IR) was used as an indicative for evaluating a similarity of dissolution profiles. The f2 value is calculated by the following equation. It was determined that each manufactured preparation had a similar dissolution profile in case that the f2 value calculated from dissolution ratio of each preparation by SUPAC-IR was in the range of $50 \leq f2 \leq 100$. Dissolution ratios at three time points such as 15 min, 30 min and 45 min after starting the test were used for a calculation of the f2 value.

[0030]

$$f2 = 50 \cdot LOG\left[\frac{100}{\sqrt{1+\frac{\sum_{i=1}^{n}(Ti-Ri)^2}{n}}}\right]$$

Ti and Ri are the percent dissolved at each point.

n is the number of points to be compared.

(3) Size distribution

A size distribution of lurasidone was measured according to a dry-spray method by Laser Diffraction Particle Size Analyzer (SLAD-3000/Shimadzu Corporation). Measuring conditions are shown below.

Amounts of sample: 2 g
Air pressure: 0.4MPa or more
Turntable rotation speed: 2
Parameter setting
Environmental setting

Monitoring average:	16	Measuring optimum range (Max):	1500
Dark measuring average:	2	(Min):	700
Light intensity display Max:	2000	(CH-1) baud rate (bps):	9600
Previous blank:	reading	Blank measurable Max:	300
Printer: monochrome		Blank measurable variation range:	20

Refractive parameter

Standard refraction:	1.70-0.20i

Measuring conditions setting

Measuring average:	1	Dry permissible Min:	300
Measuring interval (sec):	1	Max:	2500
Average:	64	Granule range for evaluation (Min):	0.1
Measured absorbance range (Max):	0.1	Granule range for evaluation (Max):	2000
(Min):	0.05	Start position of sensor usage:	1
Trigger mode:	OFF		
Dry threshold:	300		

[0031]

<Test 1>

In Examples 1, 2 and 3, tablets comprising specific pharmaceutical compositions comprising water-soluble excipient comprising 20 mg, 40 mg and 80 mg, respectively, of lurasidone per tablet, partly pregelatinized starch and water-soluble polymer binder were manufactured. In Comparative experiments 1 and 2, tablets comprising 40 mg and 80 mg, respectively, of lurasidone per tablet were manufactured on the basis of the formulation disclosed in Patent Document 2.

The manufactured preparations were subjected to the dissolution tests under conditions shown in (d) and (e), and similarities of dissolution profiles were evaluated. Additionally, preproductions in Comparative experiments 1 and 2 were shown in Test 8.

Results were shown in Tables 4 and 5. Temporal dissolution ratios in (d) were shown in Figures 2 and 3.

[0032]

(a) Formulations of granule powders

[0033]

Table 1

Unit: mg

Component	Example No.			Compar. Ex. No.	
	1	2	3	1	2
Lurasidone	80	40	20	40	80
Mannitol	144	72	36	188	148
Partly pregelatinized starch	80	40	20	-	-
Croscarmellose sodium	4	2	1	16	16
Hydroxypropyl methylcellulose	8	4	2	10	10

[0034]

(b) Formulations of granules for compression/uncoated tablets

[0035]

Table 2

Unit: mg

Component	Example No.			Compar. Ex. No.	
	1	1	1	1	2
Granules in the above (a)	316	158	79	254	254
Lactose	-	-	-	62	62
Magnesium stearate	4	2	1	4	4

[0036]

(c) Formulations of FC tablets

[0037]

Table 3

Unit: mg

Component	Example No.			Compar.Ex.No.	
	1	2	3	1	2
Uncoated tablets in the above (b)	320	160	80	320	320
Hydroxypropyl methylcellulose	3.25	1.95	1.3	2.6	2.6
Titanium oxide	1	0.6	0.4	0.8	0.8
Polyethylene glycol 6000	0.75	0.45	0.3	0.6	0.6
Carnauba wax	0.01	0.006	0.004	0.01	0.01

[0038]

(d) Dissolution test in the system comprising 80 mg of lurasidone in each vessel

Each film-coated tablet comprising 80 mg, 40 mg or 20 mg of lurasidone in the system comprising 80 mg of lurasidone in each vessel was subjected to the dissolution test, and a similarity of each dissolution profile was evaluated by f2 value.

[0039]

As evidenced by Table 4, f2 values in Examples 2 and 3 showed similarities to Example 1, but f2 value in Comparative experiment 2 did not show a similarity to Comparative experiment 1. In other words, as evidenced by Table 4 and Figure 3, in Examples 1 to 3, f2 values which represented similarities of dissolution profiles were in the range of

50≤f2≤100, and preparations which showed similarities of dissolution profiles without depending on contents in tablets (unit strength) even in preparations with different contents were obtained. On the other hand, as evidenced by Table 4 and Figure 2, dissolution of the formulation disclosed in Patent Document 2 in Comparative experiment 2 was apparently slower than that of two tablets of preparations in Comparative experiment 1, and a similarity of dissolution profile was not shown as detailed in Test 8.

[0040]

Table 4

Similarity factor	Example No.			Compar.Ex. No.	
	1	2	3	1	2
f2	-	88	97	-	37

[0041]

(e) Dissolution test in the system comprising 40 mg of lurasidone in each vessel

Each film-coated tablet comprising 40 mg or 20 mg of lurasidone in the system comprising 40 mg of lurasidone in each vessel was subjected to the dissolution test, and a similarity of each dissolution profile was evaluated by using f2 values in the similar manner.

[0042]

As evidenced by Table 5, f2 values in Example 3 and Comparative experiment 1 showed similarities to Example 2. In other words, f2 values were in the range of 50≤f2≤100 even in the system comprising 40 mg of lurasidone in each vessel, and similarities of dissolution profiles were shown without depending on contents in tablets (unit strength).

[0043]

Table 5

Similarity factor	Example No.		Compar. Ex. No.
	2	3	1
f2	-	88	97

[0044]

<Test 2>

Preparations comprising a pharmaceutical composition comprising water-soluble excipient and water-soluble polymer binder and partly pregelatinized starch were prepared in Examples 1 and 4. Preparations comprising a pharmaceutical composition comprising water-soluble excipient and water-soluble polymer binder and corn starch which was non-pregelatinized starch were prepared in Comparative experiments 3, 4 and 5. Each preparation was subjected to the dissolution test, and a similarity of each dissolution profile was evaluated by f2 value. Results were shown in Table 9.

(a) Formulations of granule powders

[0045]

Table 6

Unit: mg

Component	Example No.		Compar. Ex. No.		
	1	4	3	4	5
Lurasidone	80	80	80	80	80
Mannitol	144	176	108	108	-
Lactose	-	-	-	-	108
Partly pregelatinized starch	80	40	-	-	-
Corn starch	-	-	40	40	40
Croscarmellose sodium	4	8	16	16	16
Hydroxypropyl methylcellulose	8	12	10	10	10

[0046]

(b) Formulations of granules for compression/uncoated tablets

[0047]

Table 7

Unit: mg

Component	Example No.		Comparative Example No.		
	1	4	3	4	5
Granules in the above (a)	316	316	254	254	254
Mannitol	-	-	62	-	-
Magnesium stearate	4	4	4	4	4

[0048]

(c) Formulations of FC tablets

[0049]

Table 8

Unit: mg

Component	Example No.		Comparative Example No.		
	1	4	3	4	5
Uncoated tablets in the above (b)	320	320	320	258	258
Hydroxypropyl methylcellulose	3.25	-	2.6	2.6	2.6
Titanium oxide	1	-	0.8	0.8	0.8
Polyethylene glycol 6000	0.75	-	0.6	0.6	0.6

[0050]

(d) Dissolution test

As evidenced by Table 9, Example 4 showed a similarity to Example 1, but f2 values in Comparative experiments 3, 4 and 5 did not show similarities to Example 1. In other words, preparations containing corn starch in Comparative experiments 3, 4 and 5 showed different dissolution profiles and slow dissolutions compared to preparations containing partly pregelatinized starch in Examples 1 and 4.

[0051]

Table 9

Similarity factor	Example No.		Comparative Ex. No.		
	1	4	3	4	5
f2	-	67	44	29	26

[0052]

<Test 3>

Effects of blending quantities of partly pregelatinized starch in Examples 4, 5, 6 and 7 on dissolutions were evaluated. Results were shown in Table 13.

(a) Formulations of granule powders

[0053]

Table 10

Unit: mg

Component	Example No.				
	1	4	5	6	7
Lurasidone	80	80	80	80	80
Mannitol	144	176	116	136	156
Partly pregelatinized starch	80	40	100	80	60
Croscarmellose sodium	4	8	8	8	8
Hydroxypropyl methylcellulose	8	12	12	12	12

[0054]

(b) Formulations of granules for compression/uncoated tablets

[0055]

Table 11

Unit: mg

Component	Example No.				
	1	4	5	6	7
Granules in the above (a)	316	316	316	316	316
Magnesium stearate	4	4	4	4	4

[0056]

(c) Formulations of FC tablets

[0057]

Table 12

Unit: mg

Component	Example No.				
	1	4	5	6	7
Uncoated tablets in the above (b)	320	320	320	320	320
Hydroxypropyl methylcellulose	3.25	-	-	-	-
Titanium oxide	1	-	-	-	-
Polyethylene glycol 6000	0.75	-	-	-	-
Carnauba wax	0.01	-	-	-	-

[0058]

(d) Dissolution test

As evidenced by Table 13, f2 values in Examples 4, 5, 6 and 7 showed similarities to Example 1. In other words, a preparation comprising a pharmaceutical composition comprising 10% wt/wt or more of partly pregelatinized starch in preparation components showed a rapid dissolution and a similar dissolution profile.

[0059]

Table 13

Similarity factor	Example No.				
	1	4	5	6	7
f2	-	67	60	62	81

[0060]

<Test 4>

In Comparative experiment 6, a tablet was tried to be prepared with containing water-soluble excipient and partly pregelatinized starch but without water-soluble polymer binder. However, in a compression step, components could not be compressed due to capping and sticking, and no similar dissolution profile or even tablet was obtained. In Examples 8, 9, 10 and 11, preparations comprising pharmaceutical compositions with different blending quantities of water-soluble excipient and partly pregelatinized starch and water-soluble polymer binder were prepared. Results were shown in Table 17.

(a) Formulations of granule powders

[0061]

Table 14

Unit: mg

Component	Example No.					Compar.Ex.No.
	1	8	9	10	11	6
Lurasidone	80	80	80	80	80	80
Mannitol	144	136	138	140	142	148
Partly pregelatinized starch	80	80	80	80	80	80
Croscarmellose sodium	4	8	8	8	8	8
Hydroxypropyl methylcellulose	8	12	10	8	6	-

[0062]

(b) Formulations of granules for compression/uncoated tablets

[0063]

Table 15

Unit: mg

Component	Example No.					Compar. Ex. No.
	1	8	9	10	11	6
Granules in the above (a)	316	316	316	316	316	316
Magnesium stearate	4	4	4	4	4	4

[0064]

(c) Formulations of FC tablets

[0065]

Table 16

Unit: mg

Component	Example No.					Compar.Ex. No.
	1	8	9	10	11	6
Uncoated tablets in the above (b)	320	320	320	320	320	320
Hydroxypropyl methylcellulose	3.25	-	-	-	-	-
Titanium oxide	1	-	-	-	-	-
Polyethylene glycol 6000	0.75	-	-	-	-	-
Carnauba wax	0.01	-	-	-	-	-

[0066]

(d) Dissolution test

As evidenced by Table 17, f2 values in Examples 8, 9, 10 and 11 showed similarities to Example 1. In other words, preparations comprising pharmaceutical compositions comprising water-soluble polymer binder in the range of 1.8% wt/wt to 3.8% wt/wt showed rapid dissolutions and similar dissolution profiles.

[0067]

Table 17

Similarity factor	Example No.				
	1	8	9	10	11
f2	-	77	81	73	73

[0068]

<Test 5>

In Example 12, a preparation comprising a pharmaceutical composition comprising water-soluble polymer binder and partly pregelatinized starch was prepared by using lactose as water-soluble excipient. Results were shown in Table 21.

(a) Formulations of granule powders

[0069]

Table 18

Unit: mg

Component	Example No.		
	1	6	12
Lurasidone	80	80	80
Mannitol	144	136	-
Lactose	-	-	136
Partly pregelatinized starch	80	80	80
Croscarmellose sodium	4	8	8
Hydroxypropyl methylcellulose	8	12	12

[0070]

(b) Formulations of granules for compression/uncoated tablets

[0071]

Table 19

Unit: mg

Component	Example No.		
	1	6	12
Granules in the above (a)	316	316	316
Magnesium stearate	4	4	4

[0072]

(c) Formulations of FC tablets

[0073]

Table 20

Unit: mg

Component	Example No.		
	1	6	12
Uncoated tablets in the above (b)	320	320	320
Hydroxypropyl methylcellulose	3.25	-	-
Titanium oxide	1	-	-
Polyethylene glycol 6000	0.75	-	-
Carnauba wax	0.01	-	-

[0074]

(d) Dissolution test

As evidenced by Table 21, f2 values in Examples 6 and 12 showed similarities to Example 1. In other words, preparations containing mannitol and lactose as water-soluble excipient showed rapid dissolutions and similar dissolution profiles.

[0075]

Table 21

Similarity factor	Example No.		
	1	6	12
f2	-	62	66

[0076]

<Test 6>

In Examples 4, 13, 14 and 15, preparations comprising a specific pharmaceutical composition comprising water-soluble excipient and

water-soluble polymer binder and partly pregelatinized starch were prepared by using lurasidone bulk powders with different size distribution. Results were shown in Table 25.

(a) Size distribution of lurasidone bulk powders

D50 % (50% particle size) represents a particle size at a point where an integrated distribution calculated on the basis of volume is 50%, and D90 % (90% particle size) represents a particle size at a point where an integrated distribution calculated on the basis of volume is 90% (under sieving).

[0077]

Table 22

Unit: mg

Size distribution		Example No.			
		4	13	14	15
Particle size	D10 %	0.5	0.9	1.0	1.5
	D50 %	1.6	5.9	7.6	13.9
	D90 %	4.7	17.5	26.9	58.3

[0078]

(b) Formulations of granules for compression/uncoated tablets

[0079]

Table 23

Unit: mg

Component	Example No.			
	4	13	14	15
Lurasidone	80	80	80	80
Mannitol	176	144	144	144
Partly pregelatinized starch	40	80	80	80
Croscarmellose sodium	8	4	4	4
Hydroxypropyl methylcellulose	12	8	8	8
Magnesium stearate	4	4	4	4

[0080]

(c) Formulations of FC tablets

[0081]

Table 24

Unit: mg

Component	Example No.			
	4	13	14	15
Uncoated tablets in the above (b)	320	320	320	320
Hydroxypropyl methylcellulose	-	3.25	3.25	3.25
Titanium oxide	-	1	1	1
Polyethylene glycol 6000	-	0.75	0.75	0.75
Carnauba wax	-	0.01	0.01	0.01

[0082]

(d) Dissolution test

As evidenced by Table 25, f2 values in Examples 13, 14 and 15 showed similarities to Example 4. In other words, it was found that preparations prepared by using lurasidone bulk powders wherein 50% particle size is in the range of 1 to 8 μm and 90% particle size is 27 μm or less in size distribution showed similar dissolution profiles.

[0083]

Table 25

Similarity factor	Example No.			
	4	13	14	15
f2	-	56	56	46

[0084]

<Test 7>

Preparations wherein contents of lurasidone per tablet were 10 mg and 40 mg were manufactured by using the art disclosed in Patent Document 2, and were subjected to examination if they could provide preparations for oral administration with equivalent dissolution profiles in the range of 10 mg to 40 mg of lurasidone contents per tablet as disclosed in the document 2. Results were shown in Figure 1.

[0085]

As evidenced by Figure 1, dissolution profiles of preparations with different contents of lurasidone obtained by the art disclosed in Patent

Document 2 were shown by f2 values, and tablets with 10 mg and 40 mg of lurasidone per tablet could provide preparations for oral administration with equivalent dissolution profiles as described in Patent Document 2.

(a) Formulations of granules

[0086]

Table 26

Unit: mg

Component	10 mg tablet	40 mg tablet
Lurasidone	10	40
Mannitol	47	188
Croscarmellose sodium	4	16
Hydroxypropyl methylcellulose	2.5	10

(b) Formulations of uncoated tablets

[0087]

Table 27

Unit: mg

Component	10 mg tablet	40 mg tablet
Granules in (a)	63.5	254
Lactose	15.5	62
Magnesium stearate	1	4

(c) Formulations of FC tablets

[0088]

Table 28

Unit: mg

Component	10 mg tablet	40 mg tablet
Uncoated tablets in the above (b)	80	320
Hydroxypropyl methylcellulose	1.3	2.6
Titanium oxide	0.4	0.8
Polyethylene glycol 6000	0.3	0.6
Carnauba wax	0.006	0.01

[0089]

<Test 8>

It could be confirmed that a preparation with up to 40 mg of lurasidone per tablet could provide an oral preparation with equivalent dissolution profile in the art disclosed in Patent Document 2. A preparation wherein contents of lurasidone were 80 mg per tablet without containing partly pregelatinized starch was manufactured herein according to the art disclosed in Patent Document 2. The preparation was prepared by doubling a content ratio of the active ingredient so that a tablet weight thereof was the same as 40 mg tablet, in order to avoid an increased strain on a patient associated with growth of tablets in size. Results of Comparative experiments 1 and 2 were shown in Table 4 and Figure 2.

[0090]

As evidenced by Table 4 and Figure 2, 80 mg tablet with double content ratios of lurasidone without containing pregelatinized starch could not show equivalent dissolution to two tablets of 40 mg tablet as shown by f2 values in the art disclosed in Patent Document 2.

(a) Formulations of granules

[0091]

Table 29

Unit: mg

Component	40 mg tablet	80 mg tablet
Lurasidone	40	80
Mannitol	188	148
Croscarmellose sodium	16	16
Hydroxypropyl methylcellulose	10	10

(b) Formulations of uncoated tablets

[0092]

Table 30

Unit: mg

Component	40 mg tablet	80 mg tablet
Granules in (a)	254	254
Lactose	62	62
Magnesium stearate	4	4

(c) Formulations of FC tablets

[0093]

Table 31

Unit: mg

	40 mg tablet	80 mg tablet
Uncoated tablets in the above (b)	320	320
Hydroxypropyl methylcellulose	2.6	2.6
Titanium oxide	0.8	0.8
Polyethylene glycol 6000	0.6	0.6
Carnauba wax	0.01	0.01

[0094]

<Test 9>

Dissolutions of three kinds of preparations with different contents manufactured in Examples 1 to 3 of Test 1 were evaluated. Results were shown in Figure 3.

As evidenced by Figure 3, it was confirmed that preparations of the present invention which contained in the range of 20 mg to 80 mg of lurasidone per tablet showed equivalent dissolutions without depending on tablet contents (unit strength).

(a) Formulations of granule powders

[0095]

Table 32

Unit: mg

Component	80 mg tablet	40 mg tablet	20 mg tablet
Lurasidone	80	40	20
Mannitol	144	72	36
Partly pregelatinized starch	80	40	20
Croscarmellose sodium	4	2	1
Hydroxypropyl methylcellulose	8	4	2

(b) Formulations of granules for compression/uncoated tablets

[0096]

Table 33

Unit: mg

Component	80 mg tablet	40 mg tablet	20 mg tablet
Granules in the above (a)	316	158	79
Lactose	-	-	-
Magnesium stearate	4	2	1

(c) Formulations of FC tablets

[0097]

Table 34

Unit: mg

Component	80 mg tablet	40 mg tablet	20 mg tablet
Uncoated tablets in the above (b)	320	160	80
Hydroxypropyl methylcellulose	3.25	1.95	1.3
Titanium oxide	1	0.6	0.4
Polyethylene glycol 6000	0.75	0.45	0.3
Carnauba wax	0.01	0.006	0.004

[0098]

<Test 10>

Lurasidone 120 mg tablet preparations wherein each tablet weight was equal were prepared according to the art disclosed in the present invention as well as Patent Document 2, and dissolution profile of each preparation was evaluated.

(a) Experimental method

Lurasidone 120 mg tablet preparations were manufactured according to the preparation method of the present invention as well as Preparation method 2 in Patent Document 2 (described hereinafter) (Table 35). These manufactured preparations were subjected to the dissolution test on partly changed conditions described in C. Quality evaluation (1) dissolution test in the Example in the present specification.

The dissolution test was carried out by changing pH4.0 to pH3.8 in pH of the test solution diluted McIlvaine buffer.

[0099]

(b) Preparation method of the present invention

To a fluid bed granulator (Flow Coater FLF-30/manufactured by Freund Industrial Co., Ltd.) were charged lurasidone (8000 g), D-mannitol (14200 g), partly pregelatinized starch (8000 g) and croscarmellose sodium (400 g), and thereto was sprayed 5% hydroxypropyl methylcellulose solution previously prepared to be granulated on conditions that intake temperature was 80°C, intake airflow was 7 m^3/min, spray liquid flow rate was 200 mL/min and atomizing airflow was 200 L/min. The obtained granule was dried in the granulator on conditions that drying temperature was 80°C and drying time was 10 minutes, and it was confirmed by a halogen moisture analyzer that the loss on dry was within 2%. The obtained granule was sized by using a sizing machine (Fiore F-0 type). Then, the sized granule (18000 g) and magnesium stearate (228 g) were blended together by using a blending machine (container size 110 L) on conditions that rotation rate was 20 rpm and blending time was 5 minutes. Finally, the obtained mixture was compressed at a compressing pressure of 12.5 kN by using a compression apparatus (HT-AP12SS-II/manufactured by Hata Iron Works Co., Ltd.) to prepare

a lurasidone 120 mg uncoated tablet.

[0100]

(c) Preparation method 2 in Patent Document 2

To a fluid bed granulator (Multiplex MP-01/manufactured by Powrex Corporation) were charged lurasidone (160 g), D-mannitol (296 g) and croscarmellose sodium (32 g), and thereto was sprayed 5% hydroxypropyl methylcellulose solution previously prepared to be granulated on conditions that temperature for supplying air was 60°C and granulating time was 45 minutes. The obtained granule was dried in the granulator on conditions that drying temperature was 80°C and drying time was 5 minutes, and it was confirmed by a halogen moisture analyzer that the loss on dry was within 1%. Then, the obtained granule (254 g) and lactose (62 g) were blended together by using a blending machine (manufactured by Tsutsui Rikagaku Kikai Co., Ltd.) on conditions that rotation rate was 40 rpm and blending time was 30 minutes. After that, the resulting mixture (316 g) and magnesium stearate (4 g) were blended together by using a blending machine (manufactured by Tsutsui Rikagaku Kikai Co., Ltd.) on conditions that rotation rate was 40 rpm and blending time was 5 minutes. Finally, the obtained mixture was compressed at a compressing pressure of 12.5 kN by using a compression apparatus (HT-AP12SS-II/manufactured by Hata Iron Works Co., Ltd.) to prepare a lurasidone 120 mg uncoated tablet.

[0101]

(d) Results

Components of the manufactured preparations and results of the dissolution tests were shown below.

[0102]

Table 35

Components of tablets

Formulations	034-15-120-1000 (Disclosure of the present application)	RP-03323-120-1000 (Disclosure of Patent Document 2)
Lurasidone	120	120
Mannitol	213	222
Partly pregelatinized starch	120	-
Croscarmellose sodium	6	24
Tablettose 70	-	93
Hydroxypropyl methylcellulose	15	15
Magnesium stearate	6	6
Total	480	480

Dissolution profile

Time (min)	Dissolution rate (%)	
10	83	54
15	91	66
30	95	80
45	96	84
f2 value	-	37

As a result, it was confirmed that lurasidone 120 mg tablet manufactured according to the disclosure of the present application showed more rapid dissolution compared to lurasidone 120 mg tablet manufactured according to the disclosure of Patent Document 2.

[0103]

<Test 11>

Applied content ranges of drug substance of the present invention were evaluated on the basis of dissolution profiles of preparations.

(a) Experimental method

Lurasidone 80 mg tablets were manufactured according to the preparation method of the present invention (Table 36). These manufactured preparations were subjected to the dissolution test on conditions described in C. Quality evaluation (1) dissolution test in the Example in the present specification.

[0104]

(b) Preparation method

To a fluid bed granulator (Multiplex MP-01/manufactured by Powrex Corporation) were charged lurasidone, D-mannitol, partly pregelatinized starch and croscarmellose sodium, and thereto was sprayed 5% hydroxypropyl methylcellulose solution previously prepared to be granulated on conditions that temperature for supplying air was 60°C and granulating time was 45 minutes or 60 minutes. The obtained granule was dried in the granulator on conditions that drying temperature was 80°C and drying time was 5 minutes, and it was confirmed by a halogen moisture analyzer that the loss on dry was within 2%. Then, the obtained granule and magnesium stearate were blended together by using a blending machine (manufactured by Tsutsui Rikagaku Kikai Co., Ltd.) on conditions that rotation rate was 40 rpm and blending time was 5 minutes. Finally, the obtained mixture was compressed at a compressing pressure of 10 kN by using a compression apparatus (HT-AP12SS-II/manufactured by Hata Iron Works Co., Ltd.) to prepare a lurasidone 80 mg uncoated tablet.

[0105]

(c) Results

Components of manufactured preparations and results of dissolution tests were shown below.

[0106]

Table 36

Formulations	034-15-80-1000	RP-03320	RP-03321	RP-03322
Lurasidone	80	80	80	80
Mannitol	142	104	67	30
Partly pregelatinized starch	80	80	80	80
Croscarmellose sodium	4	4	4	4
Hydroxyproplyl methylcellulose	10	8	6	4
Magnesium stearate	4	4	3	2
Total	320	280	240	200

Dissolution profile

Time (min)	Dissolution ratio (%)			
10	85	73	71	68
15	89	80	80	81
30	93	88	88	89
45	94	90	91	91
f2 value	-	60	60	63

As a result, it could be confirmed that similar dissolution profiles were shown by components of preparations wherein lurasidone was contained in the range of 25 to 40%.

[0107]

<Test 12>

Dissolution profiles of preparations were evaluated for the water-soluble polymer binders of the present invention.

(a) Experimental method

Lurasidone 80 mg tablet was manufactured according to the preparation method of the present invention (Table 37). These manufactured preparations were subjected to the dissolution test on conditions described in C. Quality evaluation (1) dissolution test in Example in the present specification.

[0108]

(b) Preparation method

To a fluid bed granulator (Multiplex MP-01/manufactured by Powrex Corporation) were charged lurasidone (160 g), D-mannitol (284 g), partly pregelatinized starch (160 g) and croscarmellose sodium (8 g), and thereto was sprayed 5% water-soluble polymer binder solution previously prepared to be granulated on conditions that temperature for supplying air was 60°C and granulating time was 45 minutes. The obtained granule was dried in the granulator on conditions that drying temperature was 80°C and drying time was 5 minutes, and it was confirmed by a halogen moisture analyzer that the loss on dry was within 2%. Then, the obtained granule and magnesium stearate were blended together by using a blending machine (manufactured by Tsutsui Rikagaku Kikai Co., Ltd.) on conditions that rotation rate was 40 rpm and blending time was 5 minutes. Finally, the obtained mixture was compressed at a compressing pressure of 10 kN by using a compression apparatus (HT-AP12SS-II/manufactured by Hata Iron Works Co., Ltd.) to prepare a lurasidone 80 mg uncoated tablet.

[0109]

(c) Results

Components of manufactured preparations and results of dissolution tests were shown below.

[0110]

Table 37

Formulations	034-15-80-1000	RP-03326	RP-03327	RP-03328
Lurasidone	80	80	80	80
Mannitol	142	142	142	142
Partly pregelatinized starch	80	80	80	80
Croscarmellose sodium	4	4	4	4
Hydroxyproplyl methylcellulose	10	-	-	-
Polyvinylalcohol	-	10	-	-
Polyvinylpyrrolidone	-	-	10	-
Hydroxypropylcellulose	-	-	-	10
Magnesium stearate	4	4	4	4
Total	320	320	320	320

Dissolution profile

Time (min)	Dissolution ratio (%)			
10	83	59	78	80
15	91	76	82	87
30	95	94	88	91
45	96	96	90	92
f2 value	-	53	56	69

As a result, it was confirmed that preparations using as water-soluble polymer binder polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose met the standard of "C. Quality evaluation (2) Similarity of dissolution profiles" in the present specification (similar dissolution profiles).

[0111]

<Test 13>

Dissolution profiles of lurasidone 20, 40, 80 and 120 mg FC tablets prepared according to the art disclosed in the present invention were evaluated.

(a) Experimental method

Lurasidone 20, 40, 80 and 120 mg FC tablets were manufactured according to the preparation method of the present invention (Table 38).

[0112]

(b) Preparation method

To a fluid bed granulator (Flow Coater FLF-30/manufactured by Freund Industrial Co., Ltd.) were charged lurasidone (8000 g), D-mannitol (14200 g), partly pregelatinized starch (8000 g) and croscarmellose sodium (400 g), and thereto was sprayed 5% aqueous hydroxypropyl methylcellulose solution previously prepared to be granulated on conditions that intake temperature was 80°C, intake airflow was 7 m^3/min, spray liquid flow rate was 200 mL/min and atomizing airflow was 200 L/min. After spraying, the obtained granule was dried on conditions that drying temperature was 80°C and drying time was 10 minutes, and it was confirmed by a halogen moisture analyzer that the loss on dry was within 2%. The obtained granule powders were sized by using a sizing machine (Fiore F-0 type/manufactured by Tokuju Corporation). Then, the sized granule powders (18000 g) and magnesium stearate (228 g) were blended together by using a blending machine (container size 110 L/manufactured by Furukawa Altec Co., Ltd.) on conditions that rotation rate was 20 rpm and blending time was 5 minutes. The obtained powder mixtures were compressed at a compressing pressure of about 10 kN by using a compression apparatus (CLEANPRESS Correct 12HUK/manufactured by Kikusui Seisakusho Ltd. for a lurasidone 20, 40 or 80 uncoated tablet, HT-AP12SS-II/manufactured by Hata Iron Works Co., Ltd. for a lurasidone 120 mg uncoated tablet) to prepare a lurasidone 20, 40, 80 or 120 mg uncoated tablet. Then, an uncoated tablet was coated on conditions that temperature for supplying air was 80°C, airflow was 0.6 m^3/min, rotation rate of pan was 25 rpm, spray pressure was 0.15MPa and liquid flow rate was 5 g/min to give a lurasidone 20, 40, 80 or 120 mg FC tablet.

[0113]

(c) Dissolution test

Manufactured preparations were subjected to the dissolution test according to the Japanese Pharmacopoeia, Dissolution test, Method 2. Measuring conditions are shown below.

Test solution: Diluted McIlvaine buffer, pH3.8 and 4.0

Paddle rotation: 50 rpm

Test fluid: 900 ml

[0114]

(d) Results

Components of manufactured preparations and results of dissolution tests were shown below.

[0115]

Table 38

Components of tablets

Product name		Lurasidone 20 mg FC tablet	Lurasidone 40 mg FC tablet	Lurasidone 80 mg FC tablet	Lurasidone 120 mg FC tablet
Lot No.		034-15-20	034-15-40	034-15-80	034-15-120
Formulation	Lurasidone	20 mg	40 mg	80 mg	120 mg
	mannitol	35.5 mg	71 mg	142 mg	216mg
	Partly pregelatinized starch	20 mg	40 mg	80 mg	120 mg
	Croscarmellose sodium	1 mg	2 mg	4 mg	6 mg
	Hydroxypropyl methylcellulose	2.5 mg	5 mg	10 mg	15 mg
	Magnesium stearate	1 mg	2 mg	4 mg	6 mg
	Subtotal	80 mg	160 mg	320 mg	480 mg
	Hydroxypropyl methylcellulose	1.001 mg	1.690 mg	2.730 mg	1.100 mg
	Titanium oxide	0.308 mg	0.520 mg	0.840 mg	0.825 mg
	Macrogol 6000	0.231 mg	0.390 mg	0.630 mg	5.500 mg
	Carnauba wax	0.01 mg	0.01 mg	0.01 mg	0.01 mg
Total		81.55 mg	162.61 mg	324.21 mg	485.51 mg

Dissolution profile

Time (min)	Dissolution ratio (%)			
10	80	77	77	77
15	91	90	88	92
30	100	98	93	96
45	101	100	94	97
pH of test fluid	4.0	4.0	4.0	3.8

As a result, it was confirmed that lurasidone 20, 40, 80 and 120 mg FC tablets manufactured according to the disclosure of the present application showed rapid dissolutions.

[0116]

<Test 13>

Similarities of dissolution profiles were evaluated for 1 tablet of 40 mg FC tablet/2 tablets of 20 mg FC tablet, 1 tablet of 80 mg FC tablet/2

tablets of 40 mg FC tablet/4 tablets of 20 mg FC tablet, 1 tablet of 120 mg FC tablet/3 tablets of 40 mg FC tablet/6 tablets of 20 mg FC tablet.

(a) Experimental method

Preparation method and test method were abbreviated because they were similar to dissolution profiles in Test 12.

[0117]

(b) Results

Dissolution profiles of manufactured preparations and similarities thereof were shown below.

[0118]

Table 39

Tablet		40 mg tablet	20 mg tablet	80 mg tablet	40 mg tablet	20 mg tablet	120 mg tablet	40 mg tablet	20 mg tablet
Number of tablets		1 tablet	2 tablets	1 tablet	2 tablets	4 tablets	1 tablet	3 tablets	6 tablets
		Dissolution ratio (%)		Dissolution ratio (%)			Dissolution ratio (%)		
Time (min)	10	77	79	77	78	75	77	90	83
	15	90	90	88	86	84	92	94	90
	30	98	98	93	91	90	96	97	94
	45	100	100	94	93	92	97	98	95
f2 value		-	100	-	85	74	-	88	83

As a result, it was confirmed that all preparations met the standard of "C. Quality evaluation (2) Similarity of dissolution profiles" in the present specification.

INDUSTRIAL APPLICABILITY

[0119]

The present invention allows to provide a preparation for oral administration with a good disintegration which comprises as an active ingredient N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptane-dicarboxyimide hydrochloride (lurasidone), which has an equivalent dissolution profile of the active ingredient even though contents of the

active ingredient therein are varied.

BRIEF DESCRIPTION OF DRAWINGS

[0120]

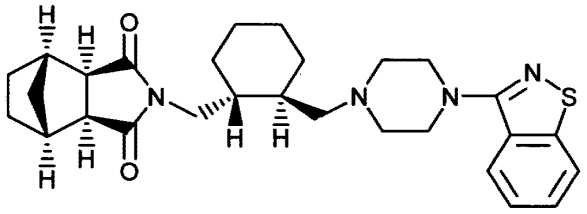
Figure 1 shows a comparison of dissolution profiles in preparations with different contents of lurasidone. Preparations wherein contents of lurasidone per tablet manufactured according to the art disclosed in Patent Document 2 were 10 mg (4 tablets) and 40 mg (1 tablet) were measured in dissolution profiles.

Figure 2 shows a comparison of dissolution profiles in preparations with different contents of lurasidone. Preparations wherein contents of lurasidone per tablet manufactured according to the art disclosed in Patent Document 2 were 40 mg (2 tablets) and 80 mg (1 tablet) were measured in dissolution profiles.

Figure 3 shows a comparison of dissolution profiles in preparations with different contents of lurasidone. Preparations wherein contents of lurasidone per tablet manufactured according to the present invention were 20 mg (4 tablets), 40 mg (2 tablets) and 80 mg (1 tablet) were measured in dissolution profiles.

CLAIMS

1. An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder.

2. An oral preparation which is prepared by granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

3. An oral preparation which is prepared by granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder.

4. The oral preparation of any one of claims 1 to 3 wherein the water-soluble excipient is mannitol or lactose.

5. A method of granulation of a powder mixture which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

6. A method of granulation of a powder mixture which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by using a solution or dispersion of lurasidone and a water-soluble polymer binder.

7. The method of granulation of claim 5 wherein the water-soluble excipient is mannitol or lactose.

8. The oral preparation of any one of claims 1 to 4 wherein the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

9. The oral preparation of any one of claims 1 to 4 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10. The oral preparation of any one of claims 1 to 4 wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt).

11. The oral preparation of any one of claims 1 to 4 wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

12. The oral preparation of any one of claims 1 to 4 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. The oral preparation of any one of claims 1 to 4 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. The oral preparation of any one of claims 1 to 4 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. The oral preparation of any one of claims 1 to 4 wherein the water-soluble excipient is mannitol or lactose and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

16. The oral preparation of any one of claims 1 to 4 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17. The oral preparation of any one of claims 1 to 4 wherein the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

18. The oral preparation of any one of claims 1 to 4 wherein the

water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

19. The oral preparation of any one of claims 1 to 4 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

20. The oral preparation of any one of claims 1 to 4 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. The oral preparation of any one of claims 1 to 4 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. The oral preparation of any one of claims 1 to 4 wherein an average particle size of lurasidone is 0.1 to 8 μm.

23. The oral preparation of any one of claims 1 to 4 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. The oral preparation of any one of claims 1 to 4 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

ABSTRACT

A preparation for oral administration comprising: a pregelatinized starch comprising N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]-heptanedicarboxyimide hydrochloride (lurasidone) represented by the formula (1) as an active ingredient; a water-soluble excipient; and a water-soluble polymeric binder, the preparation exhibiting an invariant level of elution behavior even when the content of its active ingredient is varied.

 Attorney Docket No. 0020-5610PUS1

BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. Box 747 • Falls Church, Virginia 22040-0747
Telephone: (703) 205-8000 • Facsimile: (703) 205-8050

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As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: PHARMACEUTICAL COMPOSITION

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto, the application is identified by the attorney docket number as set forth above and/or the following:

The specification was filed on _____ as United States Application Number _____; and amended on _____ (if applicable) and/or the specification was filed on May 26, 2006 as PCT International Application Number PCT/JP2006/310571; and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representative or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)			Priority Claimed	
2005-153508 (Number)	Japan (Country)	May 26, 2005 (Month/Day/Year Filed)	☒ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	☐ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	☐ Yes	☐ No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications(s) listed below.

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_____ (Application Number) _____ (Filing Date)

_____ (Application Number) _____ (Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application Number	Date of Filing (Month/Day/Year)

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Insert Prior U.S. Application(s): (if any)

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)

Attorney Docket No. 0020-5610PUSI

I hereby appoint the practitioners at **CUSTOMER NO. 02292** as my attorneys or agents to prosecute this application and/or an international application based on this application and to transact all business in the United States Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the practitioners, unless the inventor(s) or assignee provides said practitioners with a written notice to the contrary:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Full Name of First or Sole Inventor: Insert Name of Inventor → Insert Date This Document is Signed → Kazuyuki FUJIHARA	x Kazuyuki Fujihara	x 2007. Sep. 13
Residence (City, State & Country)		CITIZENSHIP
Insert Residence Insert Citizenship → Ibaraki-shi, Osaka-fu, Japan		Japan
MAILING ADDRESS (Complete Street Address including City, State & Country)		
Insert Post Office Address → c/o Dainippon Sumitomo Pharma Co., Ltd., 3-45, Kurakakiuchi 1-chome, Ibaraki-shi, Osaka 567-0878 Japan		
GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Full Name of Second Inventor, if any: see above		
Residence (City, State & Country)		CITIZENSHIP
MAILING ADDRESS (Complete Street Address including City, State & Country)		
GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Full Name of Third Inventor, if any: see above		
Residence (City, State & Country)		CITIZENSHIP
MAILING ADDRESS (Complete Street Address including City, State & Country)		
GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Full Name of Fourth Inventor, if any: see above		
Residence (City, State & Country)		CITIZENSHIP
MAILING ADDRESS (Complete Street Address including City, State & Country)		
GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Full Name of Fifth Inventor, if any: see above		
Residence (City, State & Country)		CITIZENSHIP
MAILING ADDRESS (Complete Street Address including City, State & Country)		
GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Full Name of Sixth Inventor, if any: see above		
Residence (City, State & Country)		CITIZENSHIP
MAILING ADDRESS (Complete Street Address including City, State & Country)		

*DATE OF SIGNATURE

Figure 1

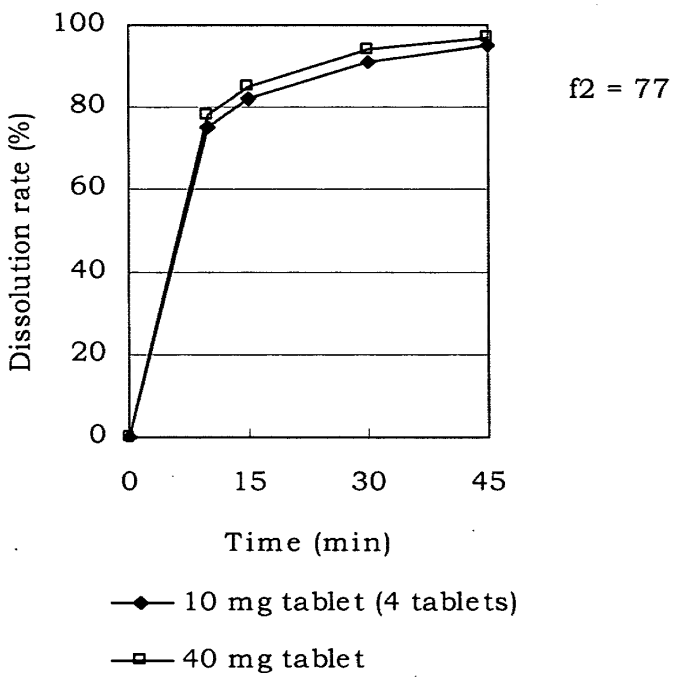

100
80
60
40
20
0
Dissolution rate (%)
0
15
30
45
Time (min)
f2 = 77
10 mg tablet (4 tablets)
40 mg tablet

Figure 2

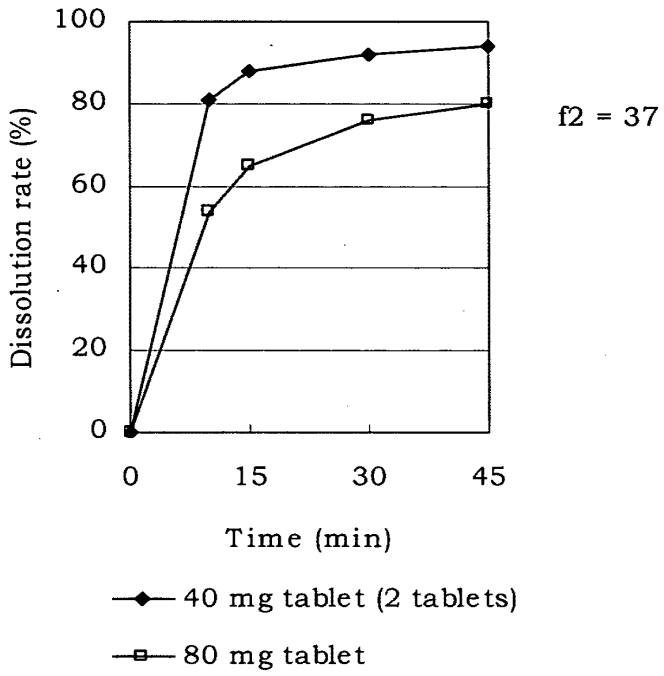
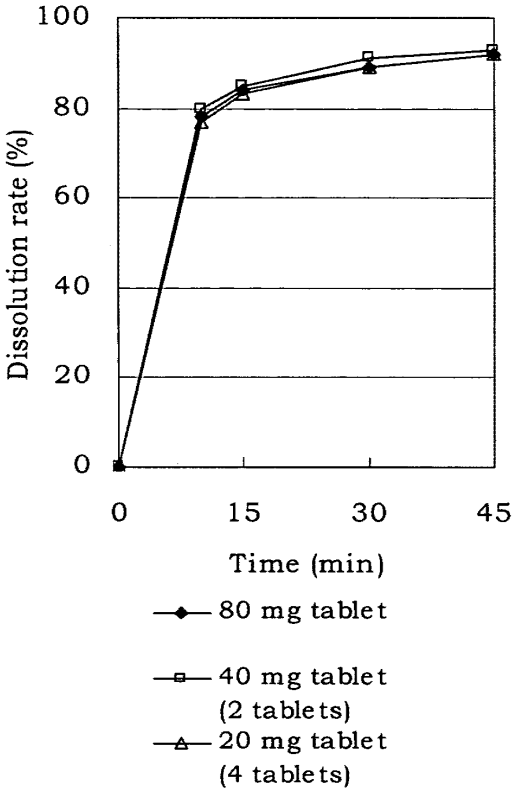

100
80
60
40
20
0
Dissolution rate (%)
0
15
30
45
Time (min)
f2 = 37
40 mg tablet (2 tablets)
80 mg tablet

Figure 3



f2 = 88
(2 tablets of 40 mg tablet for 80 mg tablet)

f2 = 97
(4 tablets of 20 mg tablet for 80 mg tablet)

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	9/20				9/20	Ｄ	
						Ｅ	
	31/645	ＡＢＮ			31/645	ＡＢＮ	
	45/00				45/00		

審査請求　未請求　請求項の数４　ＯＬ　（全 ８ 頁）　最終頁に続く

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(71)出願人　000001029
協和醗酵工業株式会社
東京都千代田区大手町１丁目６番１号

(72)発明者　上野　靖彦
静岡県三島市佐野見晴台２－１－２

(72)発明者　正田　友章
静岡県三島市加茂８－16

(72)発明者　斉藤　直浩
静岡県沼津市大岡2763－２

(54)【発明の名称】　医薬組成物

(57)【要約】

【目的】　高含量の薬物を含有する製剤において、打錠しやすく溶出性および生体への吸収性に優れた小型化された錠剤を開発する。

【構成】　微粒子化した薬物成分および界面活性剤または有機酸塩からなる核と部分アルファ化デンプンとを含有することを特徴とする医薬組成物。

1

【特許請求の範囲】

【請求項１】　微粒子化した薬物活性成分および界面活性剤または有機酸塩からなる核と部分アルファ化デンプンとを含有することを特徴とする医薬組成物。

【請求項２】　有機酸塩がクエン酸三ナトリウム、コハク酸二ナトリウム、酢酸ナトリウム、酢酸カリウムおよびグルタミン酸ナトリウムからなる群から選ばれる請求項１記載の組成物。

【請求項３】　薬物活性成分が、バルプロ酸またはその塩、マクロライド系抗生物質、スルホアミド系経口血糖降下剤、非ステロイド性抗炎症剤、サルファ剤およびトロンボキサンA₂ 拮抗剤からなる群から選ばれる請求項１または２記載の組成物。

【請求項４】　トロンボキサンA₂ 拮抗剤が１１－〔２－（５，６－ジメチル－１－ベンゾイミダゾリル）エチリデン〕－６，１１－ジヒドロジベンゾ〔ｂ，ｅ〕オキセピン－２－カルボン酸またはその塩である請求項３記載の組成物。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は崩壊性，溶出性並びに吸収性の改善された経口投与用製剤に関する。

【０００２】

【従来の技術】固形製剤、特に汎用される錠剤中の薬物活性成分を効率良く消化管から吸収させバイオアベイラビリティーを高めることは製剤学上の課題の一つである。一錠中に大量の薬物活性成分を含有する製剤は、崩壊時間が長く、溶出率が低下し、そのためバイオアベイラビリティーの低下を生じることが知られている。かかるバイオアベイラビリティーの低下を防止するために錠剤径の拡大が図られたが服用しにくいという問題がある。

【０００３】製剤学的にバイオアベイラビリティーの低下を防止する方法としては、薬物活性成分を１．有機溶媒に溶解しゼラチンカプセルに充填した軟カプセル剤とする方法、２．高分子と共に溶媒に溶解し速やかに乾燥して固体分散体とするか、または高分子と共に溶融して固体分散体とする方法、３．有機溶媒に溶解した後、多孔性物質に微粒子状に吸着させて表面積を増大する方法、４．高分子の添加剤と共に混合粉砕し非晶質とする方法、５．薬物活性成分を単独あるいは添加剤と共に粉砕し微粒子化する方法、６．界面活性剤を製剤基剤に混合する方法等があげられるが、１～４の方法は高含量化が難しい等の問題がある。

【０００４】５の微粒子化法においては、薬物活性成分のみを微粒子化した製剤（特開平５－９７６７０号公報）や、糖あるいは糖アルコールと共に混合粉砕し超微粒子化する方法（特開平３－６６６１３号公報）が知られている。また、６の界面活性剤を製剤基剤に混合することにより薬物の製剤からの放出が促進される方法が知

2

られている〔ドラック　デベロップメント　アンド　インダストリアル　ファーマシー，１６巻，１０号，１７１７頁，１９９０年；同，１２巻，６号，８５１頁，１９８６年〕。

【０００５】

【発明が解決しようとする課題】薬物微粒子の直径を小さくするほどバイオアベイラビリティーが向上するが、薬物活性成分単独では直径数μm程度にしか粉砕できず，それ以上の超微粒子を得るのは不可能である。糖あるいは糖アルコールとの混合粉砕ではサブミクロン程度の粉砕が可能であるが、糖あるいは糖アルコールが医薬品原末の５～１０倍程度必要であり、小型で薬物活性成分が高含量の製剤を得るのは難しい。また、界面活性剤を製剤基剤に混合する方法は、薬物の製剤からの放出は促進されるが打錠時にステイッキングが生じるため、製剤方法として好ましくない。

【０００６】本発明の目的は、打錠しやすく溶出性および生体への吸収性に優れた小型化された錠剤を提供することにある。

【０００７】

【課題を解決するための手段】本発明は、微粒子化した薬物活性成分および界面活性剤または有機酸塩からなる核と部分アルファ化デンプンとを含有することを特徴とする医薬組成物に関する。本発明においては、微粒子化した薬物活性成分を造粒して得た顆粒に界面活性剤または有機酸塩を噴霧して核顆粒を形成させた後、部分アルファ化デンプン等の基剤と混合して打錠するため、打錠障害が生じることなく溶出性に優れた医薬組成物が提供される。

【０００８】本発明において薬物活性成分としては、錠剤として使用されるものであればいずれでもよいが、錠剤中の含有量が多い薬物活性成分に適用するのが好ましい。例えばバルプロ酸またはその塩、アセチルスピラマイシン等のマクロライド系抗生物質、グリブゾール等のスルホアミド系経口血糖降下剤、ケトフェニルブタゾン等の非ステロイド性抗炎症剤、スルファメトピラジン等のサルファ剤、レボドパ、酢酸メドロキシプロゲストロン、１１－〔２－（５，６－ジメチル－１－ベンゾイミダゾリル）エチリデン〕－６，１１－ジヒドロジベンゾ〔ｂ，ｅ〕オキセピン－２－カルボン酸またはその塩（特開平２－９１０４１）等のトロンボキサンA₂ 拮抗剤があげられる。これら化合物の塩としては、ナトリウム塩、カリウム塩等の金属塩があげられる。本医薬組成物１錠中の薬物活性成分の含有量は通常１～８０重量％程度でよいが、好ましくは３０～８０重量％、より好ましくは３０～６０重量％である。

【０００９】薬物活性成分の微粒子化は、どのような方法を用いてもよいが、ジェット粉砕法、ハンマーミル法等により通常の高速攪拌粉砕機、衝撃粉砕機を用いて薬物活性成分を微粒子化すればよい。微粒子の径は３０μ

m以下、好ましくは１０μm以下である。

【００１０】本発明において用いられる界面活性剤は、経口製剤で許容される界面活性剤ならいかなるものでもよいが、ポリソルベート８０、ポリオキシエチレン硬化ヒマシ油６０、ショ糖脂肪酸エステル類、ラウリル硫酸ナトリウム等があげられ、好ましくはラウリル硫酸ナトリウムがあげられる。本発明で用いられる界面活性剤の添加量は、薬物活性成分に対して１～２重量％程度が好ましい。添加量が１重量％未満では効果がなく、２重量％を越えると硬度が低下し、摩損・かけの原因となる。

【００１１】本発明において用いられる有機酸塩は、経口製剤で許容される有機酸塩ならいずれでもよいが、好ましくは、クエン酸三ナトリウム、コハク酸二ナトリウム、酢酸ナトリウム、酢酸カリウム、グルタミン酸ナトリウムなどがあげられ、好ましくはクエン酸三ナトリウムが用いられる。本発明で用いられる有機酸塩の添加量は、薬物活性成分に対して０．５～４重量％、好ましくは２～４重量％である。添加量が０．５重量％未満では効果が無く、４重量％を越えるとスティッキングなどの打錠障害の原因となる。

【００１２】本発明で用いられる部分アルファ化デンプンは、トウモロコシデンプンを水と共に加熱して、でんぷん粒を破壊することなくアルファ化したものを急速に乾燥したものであればいかなるものでもよく、市販のＰＣＳ（旭化成工業株式会社製）、スターチ１５００（日本カラコン株式会社製）等があげられる。部分アルファ化デンプンは、薬物活性成分に対して通常１～４０重量％程度、好ましくは２０～３０重量％加える。

【００１３】本発明の医薬組成物は通常錠剤である。

【００１４】以下に、本発明の医薬組成物の製造方法を説明する。薬物活性成分をジェット粉砕法、ハンマーミル法等により微粒子化した後、結合剤を加えて攪拌造粒法あるいは流動層造粒法等の一般的な造粒法により核顆粒を調製し、ついで界面活性剤を２．５～５．０Ｗ／Ｖ％溶解した水溶液あるいは１．２５～１０．０Ｗ／Ｖ％の有機酸塩を含有した水溶液を流動層造粒機により該顆粒に噴霧した後、部分アルファ化デンプンおよび製剤上常用される添加剤と混合し打錠、成型する（医薬品の開発，第１１巻製剤の単位操作と機械，１９８９年広川書店刊）ことにより、本発明の医薬組成物が得られる。

【００１５】結合剤としては、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルアルコール、プルランなどが挙げられる。結合剤の添加量は薬物活性成分に対して１～３重量％、より好ましくは２～３重量％である。

【００１６】製剤上常用される添加剤としては、通常用いられる賦形剤、崩壊剤、滑沢剤等の中から主薬の安定性をそこなわず、かつ錠剤特性に影響を与えないものであればよく、例えば賦形剤としては乳糖、馬鈴薯デンプン、トウモロコシデンプン、結晶セルロース、白糖、マンニトール、炭酸カルシウム、リン酸カルシウム等があげられる。崩壊剤としては、カルボキシメチルセルロース、カルボキシメチルセルロースカルシウム、低置換度ヒドロキシプロピルセルロース、デンプングリコール酸ナトリウム、ポリビニルポリプラスドン、クロスカルメロースナトリウム等があげられる。滑沢剤としては、ステアリン酸、ステアリン酸マグネシウム、タルク、軽質無水ケイ酸、コロイド状シリカ等があげられ、これらの添加剤を単独あるいは組み合わせて用いてもよい。

【００１７】賦形剤の添加量は、薬物活性成分に対して通常０～７０％、好ましくは０～３０％であり、崩壊剤の添加量は、薬物活性成分に対して１～５０重量％、好ましくは２５～３０重量％である。滑沢剤の添加量は、薬物活性成分に対して０．５～３重量％、好ましくは１～２重量％である。

【００１８】本発明の錠剤には必要に応じて通常の剤皮を施してフィルムコーティング錠や糖衣錠、腸溶性フィルムコーティング錠とすることができる。フィルムコーティング剤皮の成分としては、水溶性高分子のヒドロキシプロピルメチルセルロース、ヒドロキシプロピルセルロース、胃溶性高分子のメタアクリル酸メチル・メタアクリル酸ブチル・メタアクリル酸ジメチル・アミノエチル共重合体〔オイラギッド(以下、 Eudragit という) E100; ロームファーマ社製（以下、Rohm Pharma という）〕、ポリビニルアセタールジエチルアミノアセテート(AEA; 三共株式会社製）、腸溶性高分子のメタアクリル酸・アクリル酸エチル共重合体(Eudragit L100-55; Rohm Pharma)、メタアクリル酸・メタアクリル酸メチル共重合体(Eudragit L100, S100; Rohm Pharma)、ヒドロキシプロピルメチルセルロースアセテートサクシネート、ヒドロキシプロプルメチルセルロースフタレート、カルボキシメチルエチルセルロース、不溶性高分子としてエチルセルロース、アクリル酸エチル・メタアクリル酸メチル・メタアクリル酸塩化トリメチル・アンモニウムエチル共重合体(Eudragit RS; Rohm Pharma) 等があげられる。糖衣成分としては、白糖、炭酸カルシウム、ゼラチン等が挙げられる。

【００１９】以下に実施例を挙げて本発明をさらに詳細に説明する。なお、これらの実施例は本発明を限定するものではない。

【００２０】

【実施例】

【００２１】実施例１（組成物１）

ジェット粉砕法により微粒化したソジウム（Ｅ）－１１－〔２－（５，６－ジメチル－１－ベンゾイミダゾリル）エチリデン〕－６，１１－ジヒドロジベンゾ〔b，e〕オキセピン－２－カルボキシレートモノハイドレート（以下、化合物Ａという）１００ｍｇをヒドロキシプロピルセルロース〔日本曹達株式会社製、（以下、HPC-L という）〕３ｍｇを用いて撹拌造粒法により造粒し核

5

顆粒を調製した。得られた核顆粒にラウリル硫酸ナトリウム〔日光ケミカルズ株式会社製（以下、SLS という）〕溶液を流動層コーティング装置を用いて、SLS が化合物Ａに対し１重量％（以下、単に％で表す）になるように噴霧した。ついで得られた該顆粒に部分アルファ化デンプン〔旭化成工業株式会社製、（以下、PCS という）〕２８．３ｍｇ、低置換度ヒドロキシプロピルセルロース〔信越化学工業株式会社製、（以下、L-HPC という）〕２７．０ｍｇ、ポリビニルポリプラスドンXL-10〔ＧＡＦケミカル社製（以下、PVPP XL-10という）〕１８．０ｍｇ、軽質無水ケイ酸〔フロイント産業製（以下、アドソリダー101 という）〕０．９ｍｇ、ステアリン酸マグネシウム〔堺化学株式会社製、（以下、Mg-St という）〕１．８ｍｇを添加し、常法により打錠して組成物１（錠剤）を得た。なお得られた錠剤の直径は８ｍｍであった。

【００２２】実施例２（組成物２）

ジェット粉砕法により微粒化した化合物Ａ１００ｍｇをポリビニルアルコール〔日本合成化学工業株式会社製（以下、PVA という）〕３．０ｍｇを用いて撹拌造粒法により造粒し核顆粒を調製した。この核顆粒に化合物Ａに対しSLS ２％となるように流動層コーティング装置を用いてSLS 溶液を噴霧した。ついでＰＣＳを２７．３ｍｇにする以外は実施例１と同様の方法で添加剤を加え組成物２（錠剤）を得た。

【００２３】実施例３（組成物３）

SLS が化合物Ａに対し１％となるように流動層コーティング装置を用いてSLS溶液を核顆粒に噴霧し、ＰＣＳを２８．３ｍｇにする以外は実施例２と同様の方法で組成物３（錠剤）を得た。

【００２４】実施例４（組成物４）

実施例１と同様の方法で化合物ＡをHPC-L を用いて撹拌造粒法で造粒し核顆粒を調製した後、得られた核顆粒にクエン酸三ナトリウムが化合物Ａに対して４％となるように流動層コーテイング装置を用いてクエン酸三ナトリウム溶液を噴霧し、ＰＣＳを２５．３ｍｇにする以外は実施例１と同様の方法により錠剤を製造し組成物４（錠剤）を得た。

【００２５】実施例５（組成物５）

クエン酸三ナトリウムを化合物Ａに対し２％となるように流動層コーティング装置を用いて噴霧し、ＰＣＳを２７．３ｍｇにする以外は実施例４と同様の方法により組成物５（錠剤）を得た。

【００２６】実施例６（組成物６）

クエン酸三ナトリウムを化合物Ａに対し１％となるように流動層コーティング装置を用いて噴霧し、ＰＣＳを２８．３ｍｇにする以外は実施例４と同様の方法により組成物６（錠剤）を得た。

【００２７】実施例７（組成物７）

クエン酸三ナトリウムを化合物Ａに対し０．５％となるように流動層コーティング装置を用いて噴霧し、ＰＣＳを２８．８ｍｇにする以外は実施例４と同様の方法により組成物７（錠剤）を得た。

6

【００２８】実施例８（組成物８）

クエン酸三ナトリウムの代わりコハク酸二ナトリウムを用いる以外は実施例４と同様の方法により組成物８（錠剤）を得た。

【００２９】実施例９（組成物９）

クエン酸三ナトリウムの代わり酢酸ナトリウムを用いる以外は実施例４と同様の方法により組成物９（錠剤）を得た。

【００３０】実施例１０（組成物１０）

クエン酸三ナトリウムの代わり酢酸カリウムを用いる以外は実施例４と同様の方法により組成物１０の錠剤を得た。

【００３１】実施例１１（組成物１１）

クエン酸三ナトリウムの代わりグルタミン酸ナトリウムを用いる以外は実施例４と同様の方法により組成物１１（錠剤）を得た。

【００３２】実施例１２（組成物１２）

実施例４で得た錠剤にあらかじめ調製したヒドロキシプロピルメチルセルロース、酸化チタン、マクロゴール6000からなるコーティング液をハイコータHC-48(フロイント産業製）を用いてコーティングし、フィルムコーティング錠を得た。

【００３３】実施例１３（組成物１３）

SLS が微粒化した化合物Ａに対し４重量％となるように流動層コーティング装置を用いてSLS 溶液を噴霧し、ＰＣＳを２５．３ｍｇにする以外は実施例３と同様の方法にて組成物１３（錠剤）を得た。

【００３４】実施例１４（組成物１４）

SLS が微粒化した化合物Ａに対し０．５重量％となるように流動層コーティング装置を用いてSLS 溶液を噴霧し、ＰＣＳを２８．８ｍｇにする以外は実施例３と同様の方法にて組成物１４（錠剤）を得た。

【００３５】参考例１（組成物ａ）

微粒化した化合物Ａ１００ｍｇをHPC-L ２ｍｇを用いて撹拌造粒法により造粒したのち直打用乳糖〔太陽化学社製；タブレトース（以下、Tablettoseという）〕２１．３ｍｇ、HPC-L ３６ｍｇ、PVPP XL-10１８ｍｇ、アドソリダー101 ０．９ｍｇ、Mg-St １．８ｍｇを添加し常法により打錠して、部分アルファ化デンプンおよび界面活性剤または有機酸の塩を添加せずに調合した組成物ａ（錠剤）を得た。得られた錠剤の直径は８ｍｍであった。

【００３６】参考例２（組成物ｂ）

微粒化した化合物Ａ１００ｍｇをHPC-L ３ｍｇを用いて撹拌造粒法により造粒したのちPCS ２９．３ｍｇ、HPC-L ２７ｍｇ、PVPP XL-10 １８ｍｇ、アドソリダー101 ０．９ｍｇ、Mg-St １．８ｍｇを添加し常法により打

7

錠して、界面活性剤または有機酸の塩を添加せずに調合した組成物ｂ（錠剤）を得た。

【００３７】参考例３（組成物ｃ）

組成物ｂを実施例１２と同じ方法で被服して組成物ｃ（被覆剤）を得た。

【００３８】参考例４（組成物ｄ）

化合物Ａおよび化合物Ａに対し４％となるようにクエン酸三ナトリウムを粉末のまま混合する以外は、実施例１で用いられている添加剤を添加した後打錠し組成物ｄ（錠剤）を得た。

【００３９】実施例および参考例で得られた各製剤について崩壊性，化合物Ａの溶出性および吸収性について比較した結果を以下に説明する。

【００４０】試験例１

8

＊実施例１で得られた組成物１、参考例１で得られた組成物ａおよび参考例２で得られた組成物ｂの崩壊試験および硬度の測定に関する比較試験を行った。また、組成物１と組成物ｂに関しては溶出試験の比較試験を行った。崩壊試験は日本薬局方第12改正一般試験法崩壊試験法に従い試験液として精製水を用いた。硬度は、錠剤破壊強度測定器（富山産業株式会社製）を用いて測定した。溶出試験は日本薬局方第12改正一般試験法溶出試験法第２法に準じ、パドル回転数を100 回転とし、試験液として精製水〔日本薬局方指定〕を用いた。

【００４１】崩壊試験及び硬度測定の結果を第１表に、溶出試験の結果を図１に示す。

【００４２】

＊　【表１】

第１表

試験項目＼組成物	組成物１	組成物ａ	組成物ｂ
硬度試験の測定硬度(Kgf)	６．３	８．５	８．２
崩壊試験の測定崩壊時間（分）	１１．０	１４．６	１８．４

【００４３】第１表によれば、組成物１は組成物ａおよび組成物ｂよりも早い崩壊時間を示した。また、図１によれば組成物１は界面活性剤を加えない組成物ｂよりも高い溶出効果を示した。

【００４４】試験例２

実施例２、３で各々得られた組成物２、３および実施例※１３、１４で得られた組成物１３、１４に関して崩壊試験および硬度の測定を試験例１に準じて行った。

【００４５】崩壊試験及び硬度測定の結果を第２表に示す。

【００４６】

【表２】

第２表

試験項目＼組成物	組成物２	組成物３	組成物13	組成物14
硬度試験の測定硬度(Kgf)	４．５	５．５	２．９	６．２
崩壊試験の測定崩壊時間（分）	１０．９	１３．５	７．２	１６．２

【００４７】試験例３

実施例４～１１で各々得られた組成物４～１１および参考例２で得られた有機酸塩を加えない組成物ｂに関して崩壊試験、硬度の測定および溶出試験の比較を試験例１に準じて行った。

【００４８】崩壊試験及び硬度測定の結果を第３表に、溶出試験の結果を図２および図３に示す。

【００４９】

【表３】

第３表

組成物	試験項目	
	硬度試験の測定硬度（Kgf）	崩壊試験の測定崩壊時間（分）精製水
4	６．８	３．０
5	７．３	５．７
6	７．２	５．６
7	６．１	９．８
8	７．４	６．０
9	７．３	４．６
１０	６．９	７．９
１１	７．１	６．９
b	７．１	１７．３

【００５０】第３表によれば各実施例組成物の水における崩壊時間は、組成物ｂよりも短かった。また図２および図３によれば各実施例組成物の溶出率はいずれも組成物ｂよりも高かった。

【００５１】試験例４

実施例１２で得られた組成物１２と参考例３で得られた組成物ｃについてビーグル犬を用いて化合物Ａの吸収性を比較した。ビーグル犬を１群５頭とし、各製剤を１錠＊30づつ水２０mlと共に投与した。経時的に採血し、血漿中の化合物Ａの濃度をHPLC法により測定した。

【００５２】化合物Ａの血漿中濃度推移を図４に薬動力学的パラメータ（血漿中濃度下面積、最高血漿中濃度）を第４表に示した。

【００５３】

【表４】

第４表

	血漿中濃度下面積（ng×h／ml）	最高血漿中濃度（ng/ml）
組成物１２	７７１．７	４７６．８
組成物ｃ	３２５．１	１７３．４

【００５４】図４によれば、クエン酸ナトリウムを添加した組成物１２は、組成物ｃよりも体内の吸収が良く、血液中の貯留時間も長かった。また、第４表によれば、組成物１２は血漿中濃度下面積（ＡＵＣ0-8h）および最高血漿中濃度（Cmax）も高かった。

【００５５】試験例５

実施例１２で得られた組成物１２と参考例３で得られた組成物ｃについて、試験例１に示した方法により溶出試験をおこなった。結果を図５に示す。図５によれば、組成物１２のほうが溶出効果が高いことが示された。

【００５６】試験例６

実施例４で得られた組成物４と参考例４で得られた組成物ｄについて、試験例１と同様の条件で崩壊試験および硬度測定を行った。結果を第５表に示す。

【００５７】

【表５】

第５表

試験項目＼組成物	組成物４	組成物ｄ
硬度(Kgf)	６．８	７．８
崩壊時間（分）	３．０	８．２

【００５８】第５表によれば、組成物４および組成物ｄの硬度に差は無いものの、組成物４では崩壊時間が大幅に増加していた。さらに、組成物４および組成物ｄの打錠性を比較したところ、組成物ｄは打錠性が悪く打錠時にステイッキングを認めた。

【００５９】

【発明の効果】本発明により、高含量の薬物を含有するにもかかわらず、打錠しやすく、溶出性および生体への吸収性に優れた小型化された製剤を得ることができる。

【図面の簡単な説明】

【図１】　組成物１と組成物ｂの溶出試験での比較

【符号の説明】

—●—　・・・・・組成物１
—○—　・・・・・組成物ｂ

【図２】　組成物４～７と組成物ｂの溶出試験での比較

【符号の説明】

—×—　・・・・・組成物４
—●—　・・・・・組成物５
—□—　・・・・・組成物６
—■—　・・・・・組成物７
—○—　・・・・・組成物ｂ

【図３】　組成物８～１１と組成物ｂの溶出試験での比較

【符号の説明】

—●—　・・・・・組成物８
—×—　・・・・・組成物９
—□—　・・・・・組成物１０
—■—　・・・・・組成物１１
—○—　・・・・・組成物ｂ

【図４】　組成物１２と組成物ｃの化合物Ａの血漿中濃度変化の比較

【符号の説明】

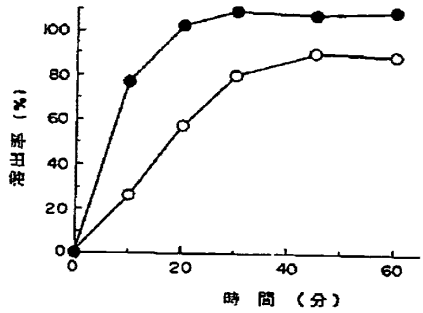
—●—　・・・・・組成物１２
—○—　・・・・・組成物ｃ

【図５】　組成物１２と組成物ｃの化合物Ａの溶出試験での比較

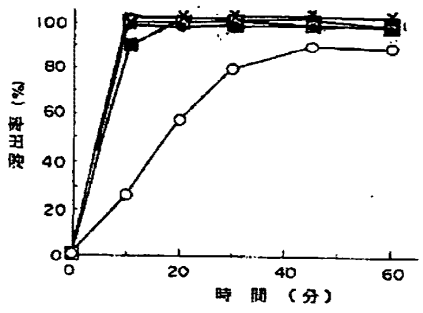
【符号の説明】

—●—　・・・・・組成物１２
—○—　・・・・・組成物ｃ

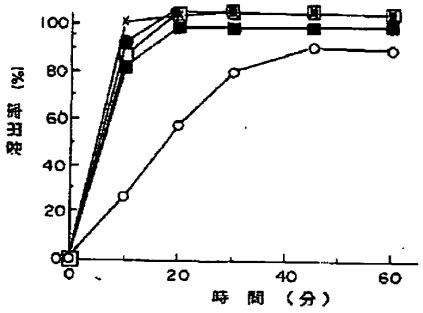
【図１】



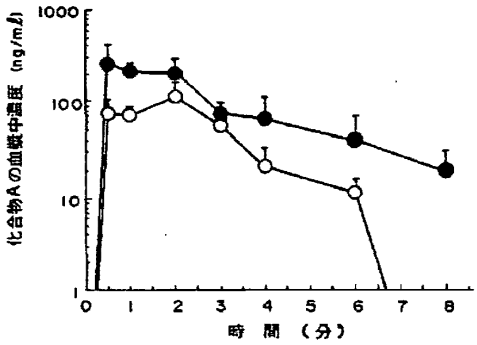
【図２】



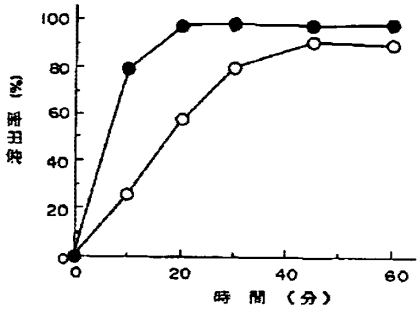
【図３】



【図４】



【図５】



フロントページの続き

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ		技術表示箇所
Ａ６１Ｋ 47/12			Ａ６１Ｋ 47/12	Ｅ	
47/16			47/16	Ｅ	
47/36			47/36	Ｂ	

WO 2006/126681
PCT/JP2006/310571

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH DO NOT APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

ISOBE, Yutaka
Intellectual Property (Kasugade), Dainippon Sumitomo Pharma Co., Ltd.
1-98, Kasugadenaka 3-chome
Konohana-ku, Osaka-shi, Osaka
5540022
JAPON

受信
19.1.11
知的財産部

Date of mailing *(day/month/year)* 28 December 2006 (28.12.2006)	
Applicant's or agent's file reference 2006012WO1 医薬の組成物 ハヒフム	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2006/310571	26 May 2006 (26.05.2006)	26 May 2005 (26.05.2005)

Applicant: Dainippon Sumitomo Pharma Co., Ltd. et al

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
30 November 2006 (30.11.2006)

   CH

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

   LU, SE, TZ, UG, ZM

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

   For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of **19 months** from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **20 MONTHS** from the priority date.

   In practice, **time limits other than the 20-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For **regular updates on the applicable time limits** (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Masashi Honda

e-mail: pt08@wipo.int

PATENT COOPERATION TREATY

WO 2006/126681
PCT/JP2006/310571

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

ISOBE, Yutaka
Intellectual Property (Kasugade), Dainippon Sumitomo Pharma Co., Ltd.
1-98, Kasugadenaka 3-chome
Konohana-ku, Osaka-shi, Osaka
5540022
JAPON

受信
19.10.-5
知的財産部

Date of mailing *(day/month/year)*	
27 September 2007 (27.09.2007)	
Applicant's or agent's file reference 2006012WO1	**IMPORTANT NOTICE**
International application No. PCT/JP2006/310571	International filing date *(day/month/year)* 26 May 2006 (26.05.2006)
Priority date *(day/month/year)* 26 May 2005 (26.05.2005)	
Applicant Dainippon Sumitomo Pharma Co., Ltd. et al	

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
30 November 2006 (30.11.2006)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, NG, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LC, LK, LR, LS, LT, LV, LY, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZM, ZW

In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Masashi Honda

e-mail: pt08.pct@wipo.int

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

ISOBE, Yutaka
Intellectual Property (Kasugade), Dainippon
Sumitomo Pharma Co., Ltd.
1-98, Kasugadenaka 3-chome
Konohana-ku, Osaka-shi, Osaka
5540022
JAPON

受信
18.8.28
知的財産部

Date of mailing *(day/month/year)* 16 August 2006 (16.08.2006)	
Applicant's or agent's file reference 2006012WO1 原薬品組成物 川上さん	IMPORTANT NOTIFICATION
International application No. PCT/JP2006/310571	International filing date *(day/month/year)* 26 May 2006 (26.05.2006)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 26 May 2005 (26.05.2005)
Applicant Dainippon Sumitomo Pharma Co., Ltd. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
26 May 2005 (26.05.2005)	2005-153508	JP	06 July 2006 (06.07.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Masashi Honda
Facsimile No. +41 22 338 70 10
Telephone No. +41 22 338 82 54

特許協力条約

Written Opinion

発信人　日本国特許庁（国際調査機関）

代理人
五十部　嶺
様

あて名
〒554-0022
日本国大阪府大阪市此花区春日出中３丁目１番９８号　大日本住友製薬株式会社　知的財産部（春日出）

受信
18.8.18
知的財産部

ＰＣＴ
国際調査機関の見解書
（法施行規則第40条の2）
〔ＰＣＴ規則43の2.1〕

発送日 （日.月.年）	１５．０８．２００６
出願人又は代理人 の書類記号　2006012W01	今後の手続きについては、下記２を参照すること。

国際出願番号	国際出願日	優先日
ＰＣＴ／ＪＰ２００６／３１０５７１	（日.月.年）　２６．０５．２００６	（日.月.年）　２６．０５．２００５

国際特許分類（ＩＰＣ）Int.Cl. ***A61K31/496*** (2006.01), ***A61K9/20*** (2006.01), ***A61K47/10*** (2006.01), ***A61K47/26*** (2006.01), ***A61K47/38*** (2006.01), ***C07D417/12*** (2006.01)

出願人（氏名又は名称）
大日本住友製薬株式会社

１．この見解書は次の内容を含む。

- ☑ 第Ⅰ欄　見解の基礎
- ☐ 第Ⅱ欄　優先権
- ☐ 第Ⅲ欄　新規性、進歩性又は産業上の利用可能性についての見解の不作成
- ☐ 第Ⅳ欄　発明の単一性の欠如
- ☑ 第Ⅴ欄　ＰＣＴ規則43の2.1(a)(i)に規定する新規性、進歩性又は産業上の利用可能性についての見解、それを裏付けるための文献及び説明
- ☐ 第Ⅵ欄　ある種の引用文献
- ☐ 第Ⅶ欄　国際出願の不備
- ☐ 第Ⅷ欄　国際出願に対する意見

２．今後の手続き
国際予備審査の請求がされた場合は、出願人がこの国際調査機関とは異なる国際予備審査機関を選択し、かつ、その国際予備審査機関がＰＣＴ規則66.1の2(b)の規定に基づいて国際調査機関の見解書を国際予備審査機関の見解書とみなさない旨を国際事務局に通知していた場合を除いて、この見解書は国際予備審査機関の最初の見解書とみなされる。

この見解書が上記のように国際予備審査機関の見解書とみなされる場合、様式ＰＣＴ／ＩＳＡ／２２０を送付した日から３月又は優先日から２２月のうちいずれか遅く満了する期限が経過するまでに、出願人は国際予備審査機関に、適当な場合は補正書とともに、答弁書を提出することができる。

さらなる選択肢は、様式ＰＣＴ／ＩＳＡ／２２０を参照すること。

３．さらなる詳細は、様式ＰＣＴ／ＩＳＡ／２２０の備考を参照すること。

見解書を作成した日
０７．０８．２００６

名称及びあて先	特許庁審査官（権限のある職員）	４Ｃ	３７５５
日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	八原　由美子 電話番号　０３－３５８１－１１０１　内線　３４５２		

様式ＰＣＴ／ＩＳＡ／237（表紙）（２００５年４月）

国際調査機関の見解書

国際出願番号　ＰＣＴ／ＪＰ２００６／３１０５７１

第Ⅰ欄　見解の基礎

1．言語に関し、この見解書は以下のものに基づき作成した。

☑ 出願時の言語による国際出願

☐ 出願時の言語から国際調査のための言語である＿＿＿＿＿＿＿＿語に翻訳された、この国際出願の翻訳文（ＰＣＴ規則12.3(a)及び23.1(b)）

2．この国際出願で開示されかつ請求の範囲に係る発明に不可欠なヌクレオチド又はアミノ酸配列に関して、以下に基づき見解書を作成した。

a．タイプ
☐ 配列表
☐ 配列表に関連するテーブル

b．フォーマット
☐ 紙形式
☐ 電子形式

c．提出時期
☐ 出願時の国際出願に含まれていたもの
☐ この国際出願と共に電子形式により提出されたもの
☐ 出願後に、調査のために、この国際調査機関に提出されたもの

3．☐ さらに、配列表又は配列表に関連するテーブルを提出した場合に、出願後に提出した配列若しくは追加して提出した配列が出願時に提出した配列と同一である旨、又は、出願時の開示を超える事項を含まない旨の陳述書の提出があった。

4．補足意見：

国際調査機関の見解書

国際出願番号　ＰＣＴ／ＪＰ２００６／３１０５７１

第Ｖ欄　新規性、進歩性又は産業上の利用可能性についてのＰＣＴ規則43の2.1(a)(i)に定める見解、それを裏付ける文献及び説明

1.　見解

新規性（N）	請求の範囲	１－２４	有
	請求の範囲		無
進歩性（ＩＳ）	請求の範囲	１－２４	有
	請求の範囲		無
産業上の利用可能性（ＩＡ）	請求の範囲	１－２４	有
	請求の範囲		無

2.　文献及び説明

国際調査報告
見解は、国際調査報告で引用された以下の各文献の記載に基づいて示された。

文献１：WO 2002/024166 A1（住友製薬株式会社）2002.03.28
文献２：WO 2004/078173 A1（塩野義製薬株式会社）2004.09.16

○請求の範囲１～２４に対して

文献１には、水難溶性の有効成分の含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示し、水難溶性の有効成分を所望の濃度に放出し得る経口製剤が記載され、A）10～40mgのルラシドン、B）マンニトール又は乳糖、及び、C）水溶性高分子結合剤を含有する経口製剤が開示されている（実施例参照）。

文献２には、錠剤全量に対し、式(I)で示される化合物もしくは製薬上許容される塩またはそれらの溶媒和物を3～80重量%、部分アルファ化デンプンを1～30重量%、乳糖を20～95重量%およびヒドロキシプロピルセルロースを0.1～5重量%含有することを特徴とする錠剤が記載され、a）40mgの化合物(I-1)、b）83mgの乳糖、c）3.0mgのヒドロキシプロピルセルロース、d）22.5mgの部分アルファ化デンプン、及び、e）1.5mgのステアリン酸マグネシウムを含有する経口製剤が優れた溶出性を示すことが開示されている（請求項３、実施例７、及び、図１参照）。

（以下、続葉に続く）

補充欄

いずれかの欄の大きさが足りない場合

第　V.2　欄の続き

本国際出願の上記請求の範囲に記載のものにおいては、ルラシドンの含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示し、ルラシドンを所望の濃度に放出し得る経口製剤を提供すべく、アルファ化デンプンを添加するものであるが、文献１及び２のいずれにもこの点について開示も示唆もされていない。

よって、請求の範囲１～２４に記載のものは、文献１及び２に対して、新規性及び進歩性を有する。

PATENT APPLICATION SERIAL NO._____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

11/05/2007 GFREY1 00000090 022448 11919678

01 FC:1631	310.00	DA
02 FC:1633	210.00	DA
03 FC:1642	410.00	DA
04 FC:1615	200.00	DA
05 FC:1614	420.00	DA

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(71) 出願人 (米国を除く全ての指定国について): 大日本住友製薬株式会社 (**Dainippon Sumitomo Pharma Co., Ltd.**) [JP/JP]; 〒5418524 大阪府大阪市中央区道修町２丁目６番８号 Osaka (JP).

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 富士原 和之 (**FUJIHARA, Kazuyuki**) [JP/JP]; 〒5670878 大阪府茨木市蔵垣内１丁目３番４５号 大日本住友製薬株式会社内 Osaka (JP).

(74) 代理人: 五十部 穣 (**ISOBE, Yutaka**); 〒5540022 大阪府大阪市此花区春日出中３丁目１番９８号 大日本住友製薬株式会社 知的財産部（春日出） Osaka, 外 (JP).

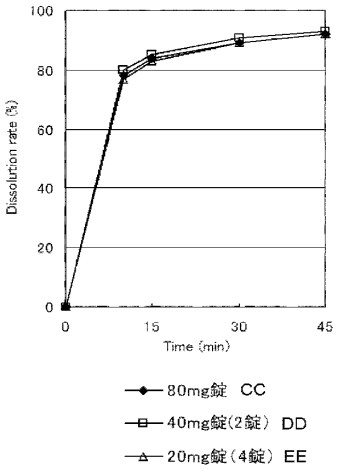
(81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU,

[続葉有]

WO 2006/126681 A1

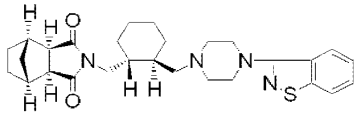
(54) Title: PHARMACEUTICAL COMPOSITION

(54) 発明の名称: 医薬品組成物



f2＝88 （80 錠に対して 40mg 錠２錠）AA
f2＝97 （80 錠に対して 20mg 錠４錠）BB

AA... (TWO 40mg-TABLETS IN PLACE OF ONE 80mg-TABLET)
BB... (FOUR 20mg-TABLETS IN PLACE OF ONE 80mg-TABLET)
CC... 80mg-TABLET
DD... 40mg-TABLET (TWO TABLETS)
EE... 20mg-TABLET (FOUR TABLETS)



・HCl (1)

(57) Abstract: A preparation for oral administration comprising: a pregelatinized starch comprising N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) represented by the formula (1) as an active ingredient; a water-soluble excipient; and a water-soluble polymeric binder, the preparation exhibiting an invariant level of elution behavior even when the content of its active ingredient is varied.

[続葉有]

ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

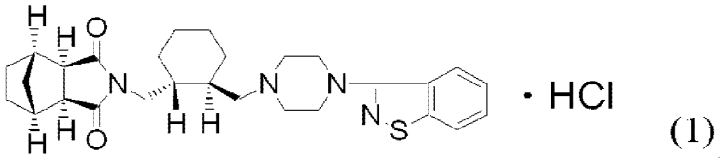
(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

２文字コード及び他の略語については、定期発行される各*PCT*ガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(57) 要約:

式(1)



(1)

で表されるN－[4－〔4－(1,2－ベンズイソチアゾール－3－イル)－1－ピペラジニル]－(2R,3R)－2,3－テトラメチレン－ブチル]－(1'R,2'S,3'R,4'S)－2,3－ビシクロ〔2,2,1〕ヘプタンジカルボキシイミド・塩酸塩(ルラシドン)を有効成分とするアルファ化デンプン類、水溶性賦形剤、水溶性高分子結合剤を含有する経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤を提供する。

明 細 書

医薬品組成物

技術分野

[0001] 本発明は、N－[4－〔4－(1,2－ベンズイソチアゾール－3－イル)－1－ピペラジニル〕－(2R,3R)－2,3－テトラメチレン－ブチル]－(1'R,2'S,3'R,4'S)－2,3－ビシクロ〔2,2,1〕ヘプタンジカルボキシイミド・塩酸塩(ルラシドン)を有効成分とする崩壊性が良好な経口製剤に関する。詳しくはルラシドンを有効成分とする経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤、特に錠剤に関する。

背景技術

[0002] 特許文献1には、ルラシドン等の化合物について、経口的に投与することができること、また通常の担体・賦形剤・結合剤・安定剤等と有効成分とを配合することにより製造できることの記載はあるが、該有効成分の含量が広い範囲で異なっても速溶解性を示し、かつ、同等の溶出挙動を示す経口用の製剤、とくに有効成分の含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示す経口製剤に関する記載はない。

[0003] 含量が異なる製剤を同一用量服用したときの生物学的同等性を保証することを目的として医薬審第64号(平成12年2月14日公布)にて『含量が異なる経口固形製剤の生物学的同等性試験ガイドライン』が示され、含量が異なる製剤において、胃、腸および口腔内の各pH値に対応するpH1.2、3.0～5.0および6.8の緩衝液、水、生理食塩水などの各試験液で同等の溶出挙動を示すことが求められるようになった。

[0004] ルラシドンを有効成分とする薬剤について、該有効成分の含量が異なっても速溶解性を示し、かつ、同等の溶出挙動を示す経口製剤、とくに有効成分の含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示し、水難溶性の有効成分を所望の濃度に放出し得る経口製剤については特許文献2に開示されている。

[0005] 特許文献2には有効成分の含量が数mg～数十mgの範囲、例えば5mg～20mgまたは5mg～40mgの範囲、で変動しても、速溶解性を示し、かつ、同一組成比にお

いて同等の溶出挙動を示す経口製剤、特に錠剤が開示されている。経口製剤においては、より高い臨床効果を得るためにさらに高い含量の製剤、又は患者の症状に応じて臨床効果を調節するためにより広い含量範囲で、複数錠と同様の挙動を示し、有効成分を所望の濃度に放出し得る製剤が必要とされる場合が多い。特許文献2の開示技術では図1に示すようにルラシドンが1錠あたり5mgから40mgまでは同等の溶出挙動を示す経口製剤を提供することができる。しかしながら、図2に示すように、製剤中の有効成分の含有率を2倍にすることにより一錠中の有効成分の含有量を増やした場合、80mg錠では同等の溶出挙動を示すことができなかった。従って、複数錠を一度に服用するか、服用に困難な大きさの錠剤にせざるを得ない状況であった。よって、水難溶性の有効成分であるルラシドンについては、高含量の経口製剤あるいはさらに広い範囲で溶出挙動が同等な経口製剤の提供は困難であった。

[0006] また、特許文献2には水溶性高分子結合剤としてデンプンが挙げられているが、アルファ化デンプンについての記載はない。アルファ化デンプンは、例えば、特許文献3に記載されているように、医薬品組成物の崩壊性及び溶出性が顕著に改善することが知られているが、非特許文献1の中でも記述されるように通常、10%以下の含有量で用いられることが多い。

[0007] 特許文献1:特許第2800953

特許文献2:WO2002／024166

特許文献3:特開2000－26292

非特許文献1:Handbook of Pharmaceutical Excipients, 2nd edition, 491, 1994, The Pharmaceutical Press

発明の開示

発明が解決しようとする課題

[0008] 本発明の目的は、ルラシドンを有効成分とし、該有効成分の含量が広い範囲で異なっても速溶解性を示し、かつ、同等の溶出挙動を示す経口用の製剤、とくに有効成分の含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示し、有効成分を所望の濃度に放出し得る経口製剤を提供することにある。

[0009] Ｎ－[4－〔4－(1,2－ベンズイソチアゾール－3－イル)－1－ピペラジニル〕－(2R,

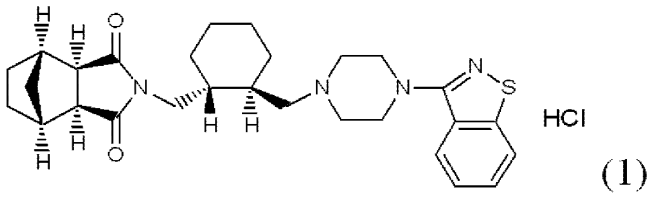
3R)－2,3－テトラメチレン－ブチル]－(1'R,2'S,3'R,4'S)－2,3－ビシクロ〔2,2,1〕ヘプタンジカルボキシイミド・塩酸塩（以下、ルラシドン）を有効成分とする経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤の提供することを目的とする。

課題を解決するための手段

[0010] 本発明者らは、前記課題を解決するために鋭意検討したところ、以下の手段により当該課題を解決することを見いだすに至った。

[0011] すなわち、本発明は、以下の通りである。

(1)式(1)

[0012] 

(1)

で表されるN－[4－〔4－(1,2－ベンズイソチアゾール－3－イル)－1－ピペラジニル〕－(2R,3R)－2,3－テトラメチレン－ブチル]－(1'R,2'S,3'R,4'S)－2,3－ビシクロ〔2,2,1〕ヘプタンジカルボキシイミド・塩酸塩（ルラシドン）、アルファ化デンプン類、水溶性賦形剤、水溶性高分子結合剤を含有する経口製剤。

(2)ルラシドン、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いて造粒した経口製剤。

(3)アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン及び水溶性高分子結合剤を溶解又は分散した液により、造粒した経口製剤。

(4)水溶性賦形剤がマンニトールもしくは乳糖である(1)～(3)いずれか記載の経口製剤。

(5)ルラシドン、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いることにより造粒する方法。

(6)アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン及び水溶性高分子結合剤を溶解又は分散した液を用いることにより造粒する方法。

(7)水溶性賦形剤がマンニトールもしくは乳糖である(5)記載の造粒方法。

(8)アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(9)アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(10)製剤中のルラシドン含有量が、20～45%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(11)製剤中のルラシドン含有量が、25～40%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(12)ルラシドンの1錠中の含量が、10～160mgである(1)から(4)いずれか記載の経口製剤。

(13)ルラシドンの1錠中の含量が、20～120mgである(1)から(4)いずれか記載の経口製剤。

(14)ルラシドンの1錠中の含量が、40～120mgである(1)から(4)いずれか記載の経口製剤。

(15)水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(16)水溶性賦形剤がマンニトールもしくは乳糖であり、製剤中のルラシドン含有量が25～40%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(17)アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(18)水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(19)水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)である(1)から(4)いずれか記載の経口製剤。

(20)水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)であり、ルラシドンの1錠中の含量が40～120mgである(1)から(4)いずれか記載の経口製剤。

(21)アルファ化デンプン類のアルファ化率が50～95%である(1)から(4)いずれか記載の経口製剤。

(22)ルラシドンの平均粒子径が0．1～8μmである(1)から(4)いずれか記載の経口製剤。

(23)アルファ化デンプン類中の水可溶分が、30%以下である(1)から(4)いずれか記載の経口製剤

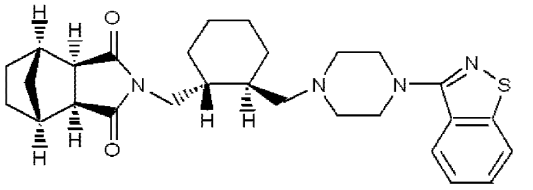
(24)水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)であり、ルラシドンの1錠中の含量が20～120 mg である(1)から(4)いずれか記載の経口製剤。

発明の効果

[0013] 特許文献2の開示技術では、1錠中にルラシドンを40mgまでしか含有しない低含有量製剤では溶出挙動をそろえた経口製剤を提供できることが確認できている。しかし、より高含有量のルラシドンを含む製剤においては、溶出挙動をそろえることができなかった。そのためルラシドンの高投与量が必要な患者においては倍量以上の低含量製剤を服用することになり、患者への負担が大きくなるため改善が求められていた。アルファ化デンプン類を含むことを特徴とする本発明製剤により、ルラシドンをより高含有量含む、患者への負担が少ない経口製剤の提供が可能となった。さらに、本発明により、ルラシドンを高含有量含む経口製剤の提供が、またルラシドンの含量が変動しても同等の溶出挙動を示す経口投与用製剤を提供することが可能となった。また、長期保存性にも優れている。

発明を実施するための最良の形態

[0014] Ｎ－[4－〔4－(1,2－ベンズイソチアゾール－3－イル)－1－ピペラジニル〕－(2R,3R)－2,3－テトラメチレン－ブチル]－(1'R,2'S,3'R,4'S)－2,3－ビシクロ〔2,2,1〕ヘプタンジカルボキシイミド・塩酸塩(ルラシドン)は下記式:

[0015] 

(1)

で示される化合物である(特許第2800953号参照)。ルラシドンは向精神病作用を持つことが知られており、統合失調症等の治療薬として有効である。本化合物の配合量としては、錠剤全重量に基づいて、例えば、10～50重量%の範囲、好ましくは20～45重量%の範囲、特に好ましくは20～45重量%の範囲から選択される。更に、微粉砕されていることが好ましく、例えば体積比90%以上の粒子が27μm以下であり、体積比による平均粒子径(50%粒子径)としては例えば、0.1～8μmの範囲が挙げられる。好ましくは、1～4μmの範囲が挙げられる。1錠中に含まれるルラシドンの含量としては、10－160mg、好ましくは20－120mg、さらに好ましくは40－120mgが挙げられる。

[0016] 「アルファ化デンプン類」とは例えばトウモロコシデンプン、バレイショデンプン、コムギデンプン、コメデンプン、タピオカデンプン等各種デンプン類をアルファ化したものであり、このようなものとしては例えば医薬品添加物規格にあるアルファ化デンプン(英語名:Pregelatinized Starch)又は部分アルファ化デンプン(英語名:Partly Pregelatinized Starch)等を挙げることができる。アルファ化デンプン類のアルファ化率は、例えば50～100%、好ましくは50～95%、さらに好ましくは80～95%である。更に、アルファ化デンプン類中の水可溶分は、例えば40%以下、より好ましくは30%以下である。これらアルファ化デンプン類は、通常、平均粒径が1～1000μm、好ましくは1～500μm、さらに好ましくは10～100μmの粉末が用いられる。本発明に適する市販のアルファ化デンプン類としては、例えばPCS(商品名、旭化成工業株式会社製)若しくはスターチ1500(商品名、カラコン)等の部分アルファ化デンプンが挙げられる。上記アルファ化デンプン類の中でも部分アルファ化デンプン、例えばPCS(商品名、旭化成工業株式会社製)が好ましく用いられる。部分アルファ化デンプンのアルファ化率は、好ましくは50～95%、さらに好ましくは80～95%である。本発明において用いられるアルファ化デンプン類は、製剤重量に対して10%以上50%以下

であり、好ましくは10%以上40%以下であり、特に好ましくは、20%以上30%以下である。

[0017] 「水溶性賦形剤」としては、例えばマンニトール、乳糖、白糖、ソルビトール、D-ソルビトール、エリスリトール、キシリトール等が挙げられる。より好ましいものとしてはマンニトール及び乳糖が挙げられる。さらに好ましくはマンニトールを挙げることができる。また、該水溶性賦形剤は、1種または同時に2種以上を使用することができる。水溶性賦形剤の配合量としては、錠剤全重量に基づいて、例えば、30～80重量%の範囲、好ましくは40～60重量%の範囲から選択される。また、マンニトールの平均粒子径としては、例えば10～200μmの範囲が挙げられる。

[0018] 「水溶性高分子結合剤」としては、例えば、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン、ポリビニルアルコール等が挙げられる。より好ましいものとしては、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン、ポリビニルアルコールが挙げられる。該水溶性高分子結合剤は、これらの1種または同時に2種類以上を用いることができる。水溶性高分子結合剤の配合量としては錠剤全重量に基づいて、例えば、0．5～10重量%の範囲、好ましくは1～5重量%の範囲から選択される。

本発明の医薬品組成物から成る経口製剤は、錠剤、カプセル剤、顆粒剤、細粒剤に製剤化されるものをいう。慣用手段によって、水溶性賦形剤に加えて非水溶性賦形剤、結合剤、崩壊剤、滑沢剤、等を使用して、錠剤、カプセル剤、顆粒剤、細粒剤に製剤化されるものであってもよい。また、以下のものを加えることもできる。

[0019] 「非水溶性賦形剤」としては、例えばコーンスターチ、結晶セルロース等が挙げられる。また、1種または同時に2種以上を使用することができる。

[0020] 「崩壊剤」としては、例えば、コーンスターチ、結晶セルロース、低置換度ヒドロキシプロピルセルロース、カルメロース、カルメロースカルシウム、カルメロースナトリウム、クロスカルメロースナトリウム、カルボキシメチルスターチナトリウム、クロスポビドン等が挙げられる。該崩壊剤は、1種または同時に2種以上を使用することができる。崩壊剤の配合量としては、錠剤全重量に基づいて、例えば、0～10重量%の範囲、好ましくは0．5～5重量%の範囲が挙げられる。

[0021] 「滑沢剤」としては、例えばステアリン酸マグネシウム、タルク、ポリエチレングリコール、シリカ、硬化植物油等が挙げられる。

[0022] 本発明の経口製剤の調製は、所望の剤形により異なるが、常法にしたがって所望の剤形にすることができる。

(1)水溶性高分子結合剤の水溶液の調製:

水溶性高分子結合剤を精製水に溶解する。水溶性高分子結合剤の量としては、精製水の量に対し、例えば1～20重量%の範囲、好ましくは2～8重量%の範囲から選択される。

(2)ルラシドン含有造粒物の調製:

ルラシドン、マンニトール、部分アルファ化デンプンを含む賦形剤および崩壊剤を仕込んだ流動層造粒機に、上記(1)の工程で調製された水溶性高分子結合剤を散布しながら造粒する。

[0023] 造粒装置としては、例えば、流動層造粒(Fluid Bed Granulation)、高速攪拌造粒(High share granulation)、転動型流動層造粒(Roto Fluid Bed Granulation)等に分類される造粒装置が挙げられる。但し、これらに限定されるものではない。

(3)造粒物の乾燥:

上記造粒物を、減圧または常圧にて乾燥する。この乾燥は、赤外線水分計にて測定される乾燥減量値が、例えば、3重量%以内、好ましくは1～2重量%以内になるように行う。

(4)滑沢剤の配合:

上記(3)で乾燥した造粒物に滑沢剤を加えて混合する。混合は、例えば、攪拌ミキサー[タンブル](Diffusion mixers [Tumble])に分類される混合機が用いられる。具体的には、タンブラーブレンダー(Tumble Blender)、Vブレンダー(V Blenders)、ダブルコーン(Double Cone)、ビンタンブラー(Bin Tumble)等が挙げられる。但し、これらに限定されるものではない。

(5)打錠:

上記混合物を打錠して錠剤を調製する。

[0024] 打錠装置としては、例えば、錠剤プレス(Tablet Press)に分類される打錠機等が挙げられる。打錠硬度としては、例えば30～200N範囲から選択される。

(6)所望によりフィルムコーティングを施す:

上記錠剤には、必要に応じてフィルムコーティングしてもよい。コーティング装置としては、例えばコーティングパンに分類される装置が挙げられる。好ましくは、通気式コーティングシステム(Perforated Coating System)で分類される装置が挙げられる。

[0025] コーティング剤としては、例えば、ヒドロキシプロピルメチルセルロース、ヒドロキシプロピルセルロース、ポリビニルピロリドン、ポリビニルアルコール等の基剤と、例えば、ポリエチレングリコール、プロピレングリコール、トリアセチン、クエン酸トリエチル、グリセリン、グリセリン脂肪酸エステル、ポリエチレングリコール等の可塑剤を組み合わせたものが挙げられる。また、必要に応じて、酸化チタン等の添加剤を加え調製することもできる。また、フィルムコーティング後に、光沢化剤としてカルナバロウ等を加えることもできる。

(7)乾燥:

上記のようにして得られた錠剤を乾燥する。乾燥は減圧または常圧で行い、赤外線水分計にて測定される乾燥減量値が、例えば、3重量%以内、好ましくは1～2重量%以内になるように行う。

[0026] 以下に本発明の実施例を挙げるが、本実施例は本発明を説明するためのものであって、本発明をなんら限定するものではない。

実施例 1

[0027] A. ルラシドンを80mg含有するフィルムコート錠(実施例1)

下記組成からなる顆粒、裸錠およびFC錠を順次調製する。尚、説明文中の括弧内に示す仕込み量は実施例1に示す処方の製剤を調製するための一例を示すものである。

原則としてこの製造方法に準じれば、その他に示す実施例についても調製できる。但し、仕込み量は処方に基づき変更する必要がある。

[0028] B. 製造方法

(1)結合液の調製(5% ヒドロキシプロピルメチルセルロース水溶液):

水溶性高分子結合剤のヒドロキシプロピルメチルセルロース(32g)を精製水(608g)に溶解し、これを結合液とした。

(2)造粒:

ルラシドン(320g)、マンニトール(576g)、部分アルファ化デンプン(320g)、クロスカルメロースナトリウム(16g)を流動層造粒機(マルチプレックスMP－01／パウレック製)に仕込み、上記(1)で調製した結合液を用いて、下記条件でスプレー造粒し造粒末を得た。得られた造粒末にステアリン酸マグネシウムを加えて混合後(40rpm、5分)に、処方(b)を有する打錠用顆粒を得た。尚、ステアリン酸マグネシウムの仕込み量は造粒末の収量に基づき処方から算出される量を混合した。

造粒条件

給気温度:60℃

風量:50－65m^3／hr

スプレー速度:13g／分

スプレーノズル径:1.2mm

スプレー圧力:0．12MPa

ガン位置:中段

(3)打錠:

上記(2)で調製した打錠用顆粒をHT-AP12SS-II(畑鉄工所)を用いて錠剤を成形した。

杵サイズ:φ10mm14R

厚み:4．20～4．30mm

打錠圧縮圧力:10KN

(4)コーティング:

上記(3)で調製した裸錠をハイコーターHCT30N(フロイント産業)で皮膜量が5mgになるように下記条件でコーティングを行い、コーティング後にカルナバロウを添加しフィルムコート錠を得た。

FC条件

給気温度　:80℃

風量　　:0.6m^3／分

パン回転数:25rpm

スプレー圧:0.15MPa

液速　　:5g／分

上述の方法により得られた製剤は以下の方法により品質を評価し、そこで得られた知見をもとに本発明を見出すに至った。

[0029] C. 品質評価

(1)溶出試験

日本薬局方溶出試験法第2法に従い、試作した製剤の溶出試験を実施した。以下に測定条件を示す。

試験溶液:希釈マックイルベイン緩衝液(diluted McIlvaine buffer、pH4.0)

パドル回転数:50rpm

試験液:900ml

(2)溶出プロファイルの類似性

溶出プロファイルの類似性を評価するための指標としてScale-Up and Past-Approval Changes for Intermediate Release Products(SUPAC-IR)に示される類似因子f2を用いた。f2は以下の式により算出される。SUPAC-IRにより各製剤の溶出率から算出されるf2値が50≦f2≦100の範囲にある場合、試作した各製剤は類似の溶出プロファイルであると判定した。また、f2値の算出に当っては試験開始後15分、30分および45分の3ポイントの時点での溶出率を用いた。

[0030]

$$f2 = 50 \cdot LOG\left[\frac{100}{\sqrt{1 + \frac{\sum_{i=1}^{n}(Ti - Ri)^2}{n}}}\right]$$

Ti and Ri are the percent dissolved at each point.

n is the number of points to be compared.

(3)粒度分布

レーザー回折粒度分布測定装置(SLAD-3000/島津製作所)の乾式噴射法にてルラシドンの粒度分布を測定した。以下に測定条件を示す。

試料量：2g
エアー圧：0.4MPa以上
ターンテーブル回転スピード：2
パラメータ設定
環境設定
モニター平均回数：16　　測定最適範囲（最大）　：1500
暗測定平均回数　：2　　（最小）　：700
光強度表示最大値：2000　　(CH-1) ボーレート(bps)：9600
前回のブランク値：読み込み　　ブランク測定許容最大値　：300
プリンター：モノクロ　　ブランク測定許容変動範囲：20
屈折率パラメーター
標準屈折率：1.70-0.20i
測定条件設定
測定回数：1　　乾式許容最小値：300
測定間隔（秒）：1　　最大値：2500
平均回数：64　　評価対象粒子範囲（最小値）：0.1
測定吸光度範囲（最大値）：0.1　　評価対象粒子範囲（最大値）：2000
（最小値）：0.05　センサ使用開始位置：1
トリガーモード：OFF
乾式しきい：300

[0031] ＜試験1＞

実施例1、2，3で、1錠中にルラシドンを20mg、40mgおよび80mg含有する水溶性賦形剤、部分アルファ化デンプンおよび水溶性高分子結合剤から成る特定の医薬品組成物を含む錠剤を試作した。また、比較例1、2で、特許文献2の開示処方に基づき1錠中にルラシドンを40mgおよび80mg含有する錠剤を試作した。

試作した製剤を(d)および(e)に示す条件で溶出試験を実施し、溶出プロファイルの類似性を評価した。なお、比較例1、2の試作については試験8にて示した。

結果は、表4，5に示した。なお、(d)については経時的な溶出率についても図2，3で示した。

[0032] (a) 造粒末の処方

[0033] [表1]

単位：ｍｇ

成分	実施例番号			比較例番号	
	1	2	3	1	2
ルラシドン	８０	４０	２０	４０	８０
マンニトール	１４４	７２	３６	１８８	１４８
部分アルファ化デンプン	８０	４０	２０	－	－
クロスカルメロースナトリウム	4	2	1	１６	１６
ヒドロキシプロピルメチルセルロース	8	4	2	１０	１０

[0034] (b) 打錠用顆粒/裸錠の処方

[0035] [表2]

単位：ｍｇ

成分	実施例番号			比較例番号	
	1	1	1	1	2
上記（ａ）の顆粒	３１６	１５８	７９	２５４	２５４
乳糖	－	－	－	６２	６２
ステアリン酸マグネシム	4	2	1	4	4

[0036] (c)FC錠の処方

[0037] [表3]

単位：ｍｇ

成分	実施例番号			比較例番号	
	1	2	3	1	2
上記(ｂ)の裸錠	３２０	１６０	８０	３２０	３２０
ヒドロキシプロピルメチルセルロース	３．２５	１．９５	１．３	２．６	２．６
酸化チタン	1	０．６	０．４	０．８	０．８
ポリエチレングリコール６０００	０．７５	０．４５	０．３	０．６	０．６
カルナバロウ	０．０１	０．００６	０．００４	０．０１	０．０１

[0038] (d) 1ベッセル当りルラシドンが80mgとなる系での溶出試験

1ベッセル当りルラシドンが80mgとなる系でルラシドンを80mg、40mgおよび20mgを含有する各フィルムコート錠の溶出試験を実施し、それぞれの溶出プロファイルの類似性をf2値により評価した。

[0039] 表4から明らかなように、実施例2,3のf2値は実施例1に対する類似性を示したが、比較例2のf2値は比較例1に対する類似性を示さなかった。即ち、表4，図3から明らかなように、実施例1乃至3は溶出プロファイルの類似性を示すf2値が50≦f2≦10

0の範囲となり、含量の異なる製剤においても、錠剤の含量（力価）に依存することなく溶出プロファイルの類似性を示す製剤が得られた。一方、表4，図2から明らかにように、詳細を試験8に記載したが、特許文献2開示処方の比較例2は比較例1からなる製剤2錠の溶出よりも明らかに遅く、溶出プロファイルの類似性は示さなかった。

[0040] [表4]

類似因子	実施例番号			比較例番号	
	1	2	3	1	2
f 2	－	８８	９７	－	３７

[0041] (e) 1ベッセル当りルラシドンが40mgとなる系での溶出試験

1ベッセル当りルラシドンが40mgとなる系でルラシドンを40mgおよび20mgを含有する各フィルムコート錠の溶出試験を実施し、それぞれの溶出プロファイルの類似性を同様にf2値を用いて評価した。

[0042] 表5から明らかなように、実施例3,比較例1のf2値は実施例2に対する類似性を示した。即ち、1ベッセル当りルラシドンが40mgである系においても、f2値は50≦f2≦100の範囲となり、錠剤の含量（力価）に依存することなく溶出プロファイルの類似性が示された。

[0043] [表5]

類似因子	実施例番号		比較例番号
	2	3	1
f 2	－	８８	９７

[0044] ＜試験2＞

実施例1および4で、水溶性賦形剤と水溶性高分子結合剤および部分アルファ化デンプンから成る医薬品組成物を含む製剤を調製した。また、比較例3，4および5で、水溶性賦形剤と水溶性高分子結合剤およびアルファ化していないデンプンであるコーンスターチから成る医薬品組成物を含む製剤を調製した。各製剤の溶出試験を実施し、溶出プロファイルの類似性をf2値により評価した。結果は、表9に示した。

(a) 造粒末の処方

[0045] [表6]

単位：ｍｇ

成分	実施例番号		比較例番号		
	1	4	3	4	5
ルラシドン	８０	８０	８０	８０	８０
マンニトール	１４４	１７６	１０８	１０８	－
乳糖	－	－	－	－	１０８
部分アルファ化デンプン	８０	４０	－	－	－
コーンスターチ	－	－	４０	４０	４０
クロスカルメロースナトリウム	4	8	１６	１６	１６
ヒドロキシプロピルメチルセルロース	8	１２	１０	１０	１０

[0046] (b) 打錠用顆粒/裸錠の処方

[0047] [表7]

単位：ｍｇ

成分	実施例番号		比較例番号		
	1	4	3	4	5
上記（ａ）の顆粒	３１６	３１６	２５４	２５４	２５４
マンニトール	－	－	６２	－	－
ステアリン酸マグネシム	4	4	4	4	4

[0048] (c)FC錠の処方

[0049] [表8]

単位：ｍｇ

成分	実施例番号		比較例番号		
	1	4	3	4	5
上記(ｂ)の裸錠	３２０	３２０	３２０	２５８	２５８
ヒドロキシプロピルメチルセルロース	３．２５	－	２．６	２．６	２．６
酸化チタン	1	－	０．８	０．８	０．８
ポリエチレングリコール６０００	０．７５	－	０．６	０．６	０．６

[0050] (d)溶出試験

表9から明らかなように、実施例4は実施例1に対する類似性を示したが、比較例3、4、5のf2値は実施例1に対して類似性を示さなかった。即ち、比較例3，4および5のコーンスターチを含む製剤は、実施例1および4の部分アルファ化デンプンを含む製剤と比較して、溶出プロファイルが異なり、溶出の遅い製剤であった。

[0051] [表9]

類似因子	実施例番号		比較例番号		
	1	4	3	4	5
ｆ２	－	６７	４４	２９	２６

[0052] ＜試験3＞

実施例4，5，6，7で、部分アルファ化デンプンの配合量の溶出性に及ぼす影響を評価した。結果は表13に示した。

(a) 造粒末の処方

[0053] [表10]

単位：ｍｇ

成分	実施例番号				
	1	4	5	6	7
ルラシドン	８０	８０	８０	８０	８０
マンニトール	１４４	１７６	１１６	１３６	１５６
部分アルファ化デンプン	８０	４０	１００	８０	６０
クロスカルメロースナトリウム	4	8	8	8	8
ヒドロキシプロピルメチルセルロース	8	１２	１２	１２	１２

[0054] (b) 打錠用顆粒/裸錠の処方

[0055] [表11]

単位：ｍｇ

成分	実施例番号				
	1	4	5	6	7
上記（ａ）の顆粒	３１６	３１６	３１６	３１６	３１６
ステアリン酸マグネシム	4	4	4	4	4

[0056] (c)FC錠の処方

[0057] [表12]

単位：ｍｇ

成分	実施例番号				
	1	4	5	6	7
上記(ｂ)の裸錠	３２０	３２０	３２０	３２０	３２０
ヒドロキシプロピルメチルセルロース	３．２５	－	－	－	－
酸化チタン	1	－	－	－	－
ポリエチレングリコール６０００	０．７５	－	－	－	－
カルナバロウ	０．０１	－	－	－	－

[0058] (d)溶出試験

表13から明らかなように、実施例4、5、6、7のf2値は実施例1に対する類似性を示した。即ち、部分アルファ化デンプンを製剤組成中の10%wt/wt以上含有する医薬

品組成物から成る製剤は、速溶解性を示し、かつ、類似の溶出プロファイルを示した。

[0059] [表13]

類似因子	実施例番号				
	1	4	5	6	7
f 2	－	６７	６０	６２	８１

[0060] ＜試験4＞

比較例6で、水溶性賦形剤と部分アルファ化デンプンを含むが、水溶性高分子結合剤を含まない錠剤の製剤化を試みたが、打錠工程において、キャッピングとスティッキングが発生し打錠できず、類似の溶出プロファイルを得るどころか錠剤すら得られなかった。実施例8,9，10および11で、水溶性賦形剤および部分アルファ化デンプンと水溶性高分子結合剤の配合量の異なる医薬品組成物を含む製剤を調製した。結果は、表17に示した。

(a) 造粒末の処方

[0061] [表14]

単位：ｍｇ

成分	実施例番号					比較例番号
	1	8	9	１０	１１	6
ルラシドン	８０	８０	８０	８０	８０	８０
マンニトール	１４４	１３６	１３８	１４０	１４２	１４８
部分アルファ化デンプン	８０	８０	８０	８０	８０	８０
クロスカルメロースナトリウム	4	8	8	8	8	8
ヒドロキシプロピルメチルセルロース	8	１２	１０	8	6	－

[0062] (b) 打錠用顆粒/裸錠の処方

[0063] [表15]

単位：ｍｇ

成分	実施例番号					比較例番号
	1	8	9	１０	１１	6
上記（ａ）の顆粒	３１６	３１６	３１６	３１６	３１６	３１６
ステアリン酸マグネシム	4	4	4	4	4	4

[0064] (c)FC錠の処方

[0065] [表16]

単位：mg

成分	実施例番号					比較例番号
	1	8	9	10	11	6
上記(b)の裸錠	320	320	320	320	320	320
ヒドロキシプロピルメチルセルコース	3．25	－	－	－	－	－
酸化チタン	1	－	－	－	－	－
ポリエチレングリコール6000	0．75	－	－	－	－	－
カルナバロウ	0．01	－	－	－	－	－

[0066] (d)溶出試験

表17から明らかなように、実施例8，9、10、11のf2値は実施例1に対する類似性を示した。即ち、水溶性高分子結合剤を1．8 %wt/wtから3．8%wt/wtの範囲において含有する医薬品組成物から成る製剤は、速溶解性を示し、かつ、類似の溶出プロファイルを示した。

[0067] [表17]

類似因子	実施例番号				
	1	8	9	10	11
f 2	—	77	81	73	73

[0068] ＜試験5＞

実施例12で、水溶性賦形剤として乳糖を用い、水溶性高分子結合剤および部分アルファ化デンプンから成る医薬品組成物を含む製剤を調製した。結果は、表21に示した。

(a) 造粒末の処方

[0069] [表18]

単位：mg

成分	実施例番号		
	1	6	12
ルラシドン	80	80	80
マンニトール	144	136	－
乳糖	－	－	136
部分アルファ化デンプン	80	80	80
クロスカルメロースナトリウム	4	8	8
ヒドロキシプロピルメチルセルロース	8	12	12

[0070] (b) 打錠用顆粒/裸錠の処方

[0071] [表19]

単位：ｍｇ

成分	実施例番号		
	1	6	12
上記（ａ）の顆粒	316	316	316
ステアリン酸マグネシム	4	4	4

[0072] (c)FC錠の処方

[0073] [表20]

単位：ｍｇ

成分	実施例番号		
	1	6	12
上記(ｂ)の裸錠	320	320	320
ヒドロキシプロピルメチルセルロース	3．25	－	－
酸化チタン	1	－	－
ポリエチレングリコール6000	0．75	－	－
カルナバロウ	0．01	－	－

[0074] (d)溶出試験

表21から明らかなように、実施例6および12のf2値は実施例1に対する類似性を示した。即ち、水溶性賦形剤としてマンニトールおよび乳糖にて速溶解性を示し、かつ、類似の溶出プロファイルを示した。

[0075] [表21]

類似因子	実施例番号		
	1	6	12
ｆ２	－	62	66

[0076] ＜試験6＞

実施例4，13，14および15で、粒度分布の異なるルラシドン原末を用いて、水溶性賦形剤と水溶性高分子結合剤および部分アルファ化デンプンから成る特定の医薬品組成物を含む製剤を調製した。結果は、表25に示した。

(a) ルラシドン原末の粒度分布

D50％(50％粒子径)とは体積基準により算出される積算分布が50％となるポイントでの粒子径を示し、D90％(90％粒子径)とは、体積基準により算出される積算分布

が90％（ふるい下）となるポイントでの粒子径を表す。

[0077] [表22]

単位：ｍｇ

粒度分布		実施例番号			
		4	１３	１４	１５
粒子径	Ｄ１０　％	０．５	０．９	１．０	１．５
	Ｄ５０　％	１．６	５．９	７．６	１３．９
	Ｄ９０　％	４．７	１７．５	２６．９	５８．３

[0078] (b) 打錠用顆粒/裸錠の処方

[0079] [表23]

単位：ｍｇ

成分	実施例番号			
	4	１３	１４	１５
ルラシドン	８０	８０	８０	８０
マンニトール	１７６	１４４	１４４	１４４
部分アルファ化デンプン	４０	８０	８０	８０
クロスカルメロースナトリウム	8	4	4	4
ヒドロキシプロピル	１２	8	8	8
メチルセルロース				
ステアリン酸マグネシウム	4	4	4	4

[0080] (c)FC錠の処方

[0081] [表24]

単位：ｍｇ

成分	実施例番号			
	4	１３	１４	１５
上記（ｂ）の裸錠	３２０	３２０	３２０	３２０
ヒドロキシプロピル	－	３．２５	３．２５	３．２５
メチルセルロース				
酸化チタン	－	1	1	1
ポリエチレングリコール	－	０．７５	０．７５	０．７５
６０００				
カルナバロウ	－	０．０１	０．０１	０．０１

[0082] (d)溶出試験

表25から明らかなように、実施例13，14、15のf2値は実施例4に対する類似性を示した。即ち、50％粒子径が1～8μｍの範囲、90％粒子径が27μｍ以下の粒度分布のルラシドン原末を用いて調製した製剤で類似の溶出プロファイルが得られるこ

とを見出した。

[0083] [表25]

類似因子	実施例番号			
	4	13	14	15
f 2	−	56	56	46

[0084] ＜試験7＞

特許文献2の開示技術を用いて1錠中のルラシドンの含有量が10mgと40mgとなる製剤を試作し、開示文献2の通り、1錠中のルラシドン含量が10mgから40mgまでは同等の溶出挙動を示す経口製剤を提供できるかどうか検証した。結果は、図1に示した。

[0085] 図1から明らかなように、特許文献2の開示技術により得られるルラシドンを異なる含有量を有する製剤の溶出プロファイルは、f2の値から明らかなように、1錠中にルラシドンを10mg含有する錠剤と40mg含有する製剤は、特許文献2のとおり同等の溶出挙動を示す経口製剤を提供できた。

(a)顆粒の処方

[0086] [表26]

単位：ｍｇ

成分	１０ｍｇ錠	４０ｍｇ錠
ルラシドン	１０	４０
マンニトール	４７	１８８
クロスカルメロースナトリウム	４	１６
ヒドロキシプロピルメチルセルロース	２．５	１０

(b)裸錠の処方

[0087] [表27]

c

単位：ｍｇ

成分	１０ｍｇ錠	４０ｍｇ錠
（ａ）の顆粒	６３．５	２５４
乳糖	１５．５	６２
ステアリン酸マグネシウム	１	４

(c)FC錠の処方

[0088] [表28]

単位：ｍｇ

成分	１０ｍｇ錠	４０ｍｇ錠
上記(ｂ)の裸錠	８０	３２０
ヒドロキシプロピルメチルセルロース	１．３	２．６
酸化チタン	０．４	０．８
ポリエチレングリコール６０００	０．３	０．６
カルナバロウ	０．００６	０．０１

[0089] ＜試験8＞

特許文献2の開示技術では1錠中にルラシドンを40mgまで含有する製剤では同等の溶出挙動を示す経口製剤を提供できることを確認できた。ここでは、特許文献2の開示技術を用いて、部分アルファー化デンプンを含まない1錠中のルラシドン含有量が80mgとなる製剤を試作した。錠剤の大型化は患者への負担を大きくするため、40mg錠と同じ錠剤重量となるように、有効成分の含有率を2倍にすることにより製した。比較例1および2の結果は表4および図2に示した。

[0090] 表4および図2から明らかなように、特許文献2の開示技術では、f2の値から明らかなように、ルラシドンの含有率を2倍にしたアルファ化デンプンを含まない80mg錠では40mg錠2錠と同等の溶出性を示すことはできなかった。

(a)顆粒の処方

[0091] [表29]

単位：ｍｇ

成分	４０ｍｇ錠	８０ｍｇ錠
ルラシドン	４０	８０
マンニトール	１８８	１４８
クロスカルメロースナトリウム	１６	１６
ヒドロキシプロピルメチルセルロース	１０	１０

(b)裸錠の処方

[0092] [表30]

単位：ｍｇ

成分	４０ｍｇ錠	８０ｍｇ錠
（ａ）の顆粒	２５４	２５４
乳糖	６２	６２
ステアリン酸マグネシウム	４	４

(c)FC錠の処方

[0093] [表31]

単位：ｍｇ

成分	４０ｍｇ錠	８０ｍｇ錠
上記(ｂ)の裸錠	３２０	３２０
ヒドロキシプロピルメチルセルロース	２．６	２．６
酸化チタン	０．８	０．８
ポリエチレングリコール６０００	０．６	０．６
カルナバロウ	０．０１	０．０１

[0094] ＜試験９＞

試験1の実施例1～3にて試作した含量の異なる3種類の製剤の溶出性を評価した。結果は、図3に示した。

図3から明らかなように、本発明により1錠中にルラシドンを20mgから80mgを含有する製剤においても、錠剤の含量(力価)に依存しない同等の溶出性が確認された。

(a) 造粒末の処方

[0095] [表32]

単位：ｍｇ

成分	８０ｍｇ錠	４０ｍｇ錠	２０ｍｇ錠
ルラシドン	８０	４０	２０
マンニトール	１４４	７２	３６
部分アルファ化デンプン	８０	４０	２０
クロスカルメロースナトリウム	4	2	1
ヒドロキシプロピルメチルセルロース	8	4	2

(b) 打錠用顆粒/裸錠の処方

[0096] [表33]

単位：ｍｇ

成分	８０ｍｇ錠	４０ｍｇ錠	２０ｍｇ錠
上記（ａ）の顆粒	３１６	１５８	７９
乳糖	—	—	—
ステアリン酸マグネシウム	4	2	1

(c)FC錠の処方

[0097] [表34]

単位：ｍｇ

成分	８０ｍｇ錠	４０ｍｇ錠	２０ｍｇ錠
上記(ｂ)の裸錠	３２０	１６０	８０
ヒドロキシプロピルメチルセルロース	３．２５	１．９５	１．３
酸化チタン	１	０．６	０．４
ポリエチレングリコール６０００	０．７５	０．４５	０．３
カルナバロウ	０．０１	０．００６	０．００４

[0098] ＜試験10＞

本願発明の開示技術並びに特許文献2の開示技術を用いて、錠剤重量がそれぞれ等しいルラシドン 120mg錠を作製し、両製剤の溶出挙動を評価した。

(a)実験方法

本願発明の製造方法ならびに特許文献2の製造方法2(以下に記載)に基づいてルラシドン 120mg錠製剤を試作した(表35)。これら試作した製剤について本願明細書実施例のC.品質評価(1)溶出試験に記載の条件を一部変更して溶出試験を実施した。

溶出試験は、試験溶液である希釈マックイルベイン緩衝液のpHをpH4.0からpH3.8に変更して実施した。

[0099] (b)本願発明の製造方法

ルラシドン 8000g、D-マンニトール 14200g、部分α化デンプン 8000g、クロスカルメロースナトリウム 400gを、流動層造粒機(フローコーター FLF－30／フロイント産業)に仕込み、あらかじめ調製しておいた5% ヒドロキシプロピルメチルセルロース溶液を散布しながら、吸気温度80℃、吸気風量 7 m^3/min、スプレー液速度200mL/min、アトマイズエアー流量 200L/minという条件で造粒した。得られた造粒物を造粒機内で、乾燥温度80℃、乾燥時間10分という条件で乾燥し、乾燥減量値が2%以内となっていることをハロゲン水分計で確認した。得られた造粒物は整粒機(フィオーレF-0型)を用いて整粒した。次に得られた整粒物18000gとステアリン酸マグネシウム 228gを、混合機(コンテナーサイズ110 L)を用いて回転数20rpm、混合時間5分という条件で混合した。最後に得られたこの混合物を、打錠機(HT-AP12SS-II／畑鉄工所)を用いて打錠圧12.5kNで打錠してルラシドン 120mg錠裸錠を作製した。

[0100] (c)特許文献2の製造方法2

ルラシドン 160g、D-マンニトール 296g、クロスカルメロースナトリウム 32gを、流動層造粒機(マルチプレックスMP-01／パウレック)に仕込み、あらかじめ調製しておいた5%ヒドロキシプロピルメチルセルロース溶液を散布しながら、給気温度60℃、造粒時間45分という条件で造粒した。得られた造粒物を造粒機内で、乾燥温度80℃、乾燥時間5分という条件で乾燥し、乾燥減量値が1%以内となっていることをハロゲン水分計で確認した。次に得られた造粒物254gと乳糖62gを、混合機(筒井理化学器械)を用いて回転数40rpm、混合時間30分という条件で混合した。その後、得られた混合物316gとステアリン酸マグネシウム 4gを、混合機(筒井理化学器械)を用いて回転数40rpm、混合時間5分という条件で混合した。最後に得られたこの混合物を、打錠機(HT-AP12SS-II／畑鉄工所)を用いて打錠圧12.5kNで打錠してルラシドン 120mg錠裸錠を作製した。

[0101] (d)実験結果

試作した製剤の組成と溶出試験の結果を以下に示す。

[0102] [表35]

錠剤の組成

処方	034-15-120-1000	RP-03323-120-1000
	(本出願の開示技術)	(特許文献2の開示技術)
ルラシドン	１２０	１２０
マンニトール	２１３	２２２
部分α化デンプン	１２０	－
クロスカルメロースナトリウム	６	２４
タブレトース70	－	９３
ヒドロキシプロピルメチルセルロース	１５	１５
ステアリン酸マグネシウム	６	６
合計	４８０	４８０
溶出挙動		
時間 (分)	溶出率(%)	
10	８３	５４
15	９１	６６
30	９５	８０
45	９６	８４
f2値	－	３７

この結果、特許文献2の開示技術を基に試作したルラシドン 120mg錠と比較して、本出願の開示技術を基に試作したルラシドン 120mg錠が速溶解性を示すことが確認された。

[0103] ＜試験11＞

本願発明の原薬含量の適用範囲について、製剤の溶出挙動を基に評価した。

(a)実験方法

本願発明の製造方法に基づいてルラシドン 80mg錠を試作した（表36）。これら試作した製剤について本願明細書実施例のC.品質評価(1)溶出試験に記載の条件で溶出試験を実施した。

[0104] (b)製造方法

ルラシドン、D-マンニトール、部分α化デンプン、クロスカルメロースナトリウムを、流動層造粒機（マルチプレックスMP-01／パウレック）に仕込み、あらかじめ調製しておいた5% ヒドロキシプロピルメチルセルロース溶液を散布しながら、給気温度60℃、造粒時間45分あるいは60分という条件で造粒した。得られた造粒物を造粒機内で、乾燥温度80℃、乾燥時間5分という条件で乾燥し、乾燥減量値が2%以内となっていることをハロゲン水分計で確認した。次に得られた造粒物とステアリン酸マグネシウムを、混合機（筒井理化学器械）を用いて回転数40rpm、混合時間5分という条件で混合した。最後に得られたこの混合物を、打錠機（HT-AP12SS-II／畑鉄工所）を用いて打錠圧10kNで打錠してルラシドン 80mg錠裸錠を作製した。

[0105] (c)実験結果

試作した製剤の組成と溶出試験の結果を以下に示した。

[0106] [表36]

処方	034-15－80－1000	RP-03320	RP-03321	RP-03322
ルラシドン	８０	８０	８０	８０
マンニトール	１４２	１０４	６７	３０
部分α化デンプン	８０	８０	８０	８０
クロスカルメロースナトリウム	４	４	４	４
ヒドロキシプロピルメチルセルロース	１０	８	６	４
ステアリン酸マグネシウム	４	４	３	２
合計	３２０	２８０	２４０	２００
溶出挙動				
時間（分）	溶出率（%）			
１０	８５	７３	７１	６８
１５	８９	８０	８０	８１
３０	９３	８８	８８	８９
４５	９４	９０	９１	９１
ｆ２値	－	６０	６０	６３

この結果、ルラシドンの製剤中の含有量としては25～40%の範囲で類似の溶出プロファイルを示す製剤組成であることが確認できた。

[0107] ＜試験12＞

本願発明の水溶性高分子結合剤について、製剤の溶出挙動を評価した。

(a)実験方法

本願発明の製造方法に基づいてルラシドン 80mg錠を試作した（表37）。これら試作した製剤について本願明細書実施例のC.品質評価(1)溶出試験に記載の条件で溶出試験を実施した。

[0108] (b)製造方法

ルラシドン 160 g、D-マンニトール 284 g、部分α化デンプン160 g、クロスカルメロースナトリウム 8 gを、流動層造粒機（マルチプレックスMP-01／パウレック）に仕込み、あらかじめ調製しておいた5% 水溶性高分子結合剤溶液を散布しながら、給気温度60℃、造粒時間45分という条件で造粒した。得られた造粒物を造粒機内で、乾燥温度80℃、乾燥時間5分という条件で乾燥し、乾燥減量値が2%以内となっていることをハロゲン水分計で確認した。次に得られた造粒物とステアリン酸マグネシウムを、混合機（筒井理化学器械）を用いて回転数40rpm、混合時間5分という条件で混合した。最後に得られたこの混合物を、打錠機（HT-AP12SS-II／畑鉄工所）を用いて打錠圧10kNで打錠してルラシドン 80mg錠裸錠を作製した。

[0109] (c)実験結果

試作した製剤の組成と溶出試験の結果を以下に示す。

[0110] [表37]

錠剤の組成

処方	034-15－80－1000	RP-03326	RP-03327	RP-03328
ルラシドン	８０	８０	８０	８０
マンニトール	１４２	１４２	１４２	１４２
部分α化デンプン	８０	８０	８０	８０
クロスカルメロースナトリウム	４	４	４	４
ヒドロキシプロピルメチルセルロース	１０	－	－	－
ポリビニルアルコール	－	１０	－	－
ポリビニルピロリドン	－	－	１０	－
ヒドロキシプロピルセルロース	－	－	－	１０
ステアリン酸マグネシウム	４	４	４	４
合計	３２０	３２０	３２０	３２０

溶出挙動

時間（分）	溶出率(%)			
１０	８３	５９	７８	８０
１５	９１	７６	８２	８７
３０	９５	９４	８８	９１
４５	９６	９６	９０	９２
ｆ２値	－	５３	５６	６９

この結果、水溶性高分子結合剤にポリビニルアルコール、ポリビニルピロリドン、ヒドロキシプロピルセルロースを用いた製剤においても、本明細書P.6「C．品質評価(2)溶出プロファイルの類似性」の基準を満たす製剤(類似の溶出プロファイル)となることを確認した。

[0111] ＜試験13＞

本願発明の開示技術を用いて作製したルラシドン 20、40、80、120 mg錠FC錠の溶出挙動を評価した。

(a)実験方法

本願発明の製造方法に基づいてルラシドン 20、40、80、120 mg錠FC錠を試作した(表38)。

[0112] (b)製造方法

ルラシドン 8000g、D-マンニトール 14200g、部分α化デンプン 8000g、クロスカルメロースナトリウム 400gを、流動層造粒機(フローコーター FLF－30／フロイント産業)に仕込み、あらかじめ調製しておいた5% ヒドロキシプロピルメチルセルロース水溶液を散布しながら、吸気温度80℃、吸気風量 7 m^3/min、スプレー液速度200 mL/min、アトマイズエアー流量 200 L/minという条件で造粒した。スプレー終了後、乾燥温度80℃、乾燥時間10分という条件で乾燥し、乾燥減量値が2%以内となっていることをハロゲン水分計で確認した。得られた造粒末は整粒機(フィオーレF-0型／徳寿工作所)を用いて整粒した。次に得られた整粒末18000gとステアリン酸マグネシウム 228gを、混合機(コンテナーサイズ110 L／古河アルテック)を用いて回転数20rpm、混合時間5分という条件で混合した。得られたこの混合末を、打錠機(ルラシドン 20、40、80錠裸錠についてはCLEANPRESS Correct 12HUK／菊水製作所、ルラシドン 120mg錠裸錠についてはHT-AP12SS-II／畑鉄工所)を用いて打錠圧約10kNで打錠してルラシドン 20、40、80、120mg錠裸錠を作製した。次に、給気温度80℃、風量0.6m^3/min、パン回転数25rpm、スプレー圧0.15MPa、液速5g/minという条件で裸錠をコーティングしてルラシドン 20、40、80、120mg錠FC錠を得た。

[0113] (c)溶出試験

日本薬局方溶出試験法第2法に従い、試作した製剤の溶出試験を実施した。以下に測定条件を示す。

試験溶液:希釈マックイルベイン緩衝液(diluted McIlvaine buffer、pH3．8および4．0)

パドル回転数:50rpm

試験液:900ml

[0114] (d)実験結果

試作した製剤の組成と溶出試験の結果を以下に示した。

[0115] [表38]

錠剤の組成

品名		ルラシドン 20mg錠 FC錠	ルラシドン 40mg錠 FC錠	ルラシドン 80mg錠 FC錠	ルラシドン 120mg錠 FC錠
Lot No.		034-15-20	034-15-40	034-15-80	034-15-120
処方	ルラシドン	20mg	40mg	80mg	120mg
	マンニトール	35.5mg	71mg	142mg	216mg
	部分α化デンプン	20mg	40mg	80mg	120mg
	クロスカルメロースナトリウム	1mg	2mg	4mg	6mg
	ヒドロキシプロピルメチルセルロース	2.5mg	5mg	10mg	15mg
	ステアリン酸マグネシウム	1mg	2mg	4mg	6mg
	小計	80mg	160mg	320mg	480mg
	ヒドロキシプロピルメチルセルロース	1.001mg	1.690mg	2.730mg	1.100mg
	酸化チタン	0.308mg	0.520mg	0.840mg	0.825mg
	マクロゴール6000	0.231mg	0.390mg	0.630mg	5.500mg
	カルナウバロウ	0.01mg	0.01mg	0.01mg	0.01mg
合計		81.55mg	162.61mg	324.21mg	485.51mg

溶出挙動

時間（分）	溶出率（%）			
10	80	77	77	77
15	91	90	88	92
30	100	98	93	96
45	101	100	94	97
試験液のpH	4.0	4.0	4.0	3.8

この結果、本出願の開示技術を基に試作したルラシドン 20,40,80,120mg錠FC錠が速溶解性を示すことが確認された。

[0116] ＜試験13＞

40 mg錠FC錠1錠／20 mg錠FC錠2錠、80 mg錠FC錠1錠／40 mg錠FC錠2錠／20 mg錠FC錠4錠、120 mg錠FC錠1錠／40 mg錠FC錠3錠／20 mg錠FC錠6錠の溶出挙動の類似性を評価した。

(a)実験方法

製造方法、試験方法は、試験12の溶出挙動」と同様なので省略した。

[0117] (b)実験結果

試作した製剤の溶出挙動とその類似性を以下に示した。

[0118] [表39]

錠剤		40mg錠	20mg錠	80mg錠	40mg錠	20mg錠	120mg錠	40mg錠	20mg錠
錠剤数		1錠	2錠	1錠	2錠	4錠	1錠	3錠	6錠
		溶出率(%)		溶出率(%)			溶出率(%)		
時間(分)	10	77	79	77	78	75	77	90	83
	15	90	90	88	86	84	92	94	90
	30	98	98	93	91	90	96	97	94
	45	100	100	94	93	92	97	98	95
f2値		-	100	-	85	74	-	88	83

この結果、すべての製剤において本明細書P.6「C. 品質評価(2)溶出プロファイルの類似性」の基準を満たすことが確認された。

産業上の利用可能性

[0119] 本発明によりN－[4－〔4－(1,2－ベンズイソチアゾール－3－イル)－1－ピペラジニル〕－(2R,3R)－2,3－テトラメチレン－ブチル]－(1'R,2'S,3'R,4'S)－2,3－ビシクロ〔2,2,1〕ヘプタンジカルボキシイミド・塩酸塩(ルラシドン)を有効成分とする崩壊性が良好な経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤を提供することが可能となった。

図面の簡単な説明

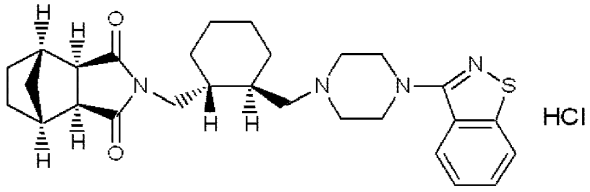
[0120] [図1]図1はルラシドンを異なる含有量を有する製剤の溶出プロファイルの比較を示したものである。特許文献2の開示技術を用いて試作した1錠中のルラシドンの含有量が10mg(4錠)と40mg(1錠)の製剤について溶出プロファイルを測定した。

[図2]図2は、ルラシドンを異なる含有量を有する製剤の溶出プロファイルの比較を示したものである。特許文献2の開示技術を用いて試作した1錠中のルラシドンの含有量が40mg(2錠)と80mg(1錠)の製剤について溶出プロファイルを測定した。

[図3]図3は、ルラシドンを異なる含有量を有する製剤の溶出プロファイルの比較を示したものである。本発明の技術を用いて試作した1錠中のルラシドンの含有量が20mg(4錠)、40mg(2錠)と80mg(1錠)の製剤について溶出プロファイルを測定した。

請求の範囲

[1] 式(1)



(1)

で表されるN－[4－〔4－(1,2－ベンズイソチアゾール－3－イル)－1－ピペラジニル〕－(2R,3R)－2,3－テトラメチレン－ブチル]－(1'R,2'S,3'R,4'S)－2,3－ビシクロ〔2,2,1〕ヘプタンジカルボキシイミド・塩酸塩(ルラシドン)、アルファ化デンプン類、水溶性賦形剤、水溶性高分子結合剤を含有する経口製剤。

[2] ルラシドン、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いて造粒した経口製剤。

[3] アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン及び水溶性高分子結合剤を溶解又は分散した液により、造粒した経口製剤。

[4] 水溶性賦形剤がマンニトールもしくは乳糖である請求項1～3いずれか記載の経口製剤。

[5] ルラシドン、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いることにより造粒する方法。

[6] アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン及び水溶性高分子結合剤を溶解又は分散した液を用いることにより造粒する方法。

[7] 水溶性賦形剤がマンニトールもしくは乳糖である請求項5記載の造粒方法。

[8] アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[9] アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[10] 製剤中のルラシドン含有量が、20～45%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[11] 製剤中のルラシドン含有量が、25～40%(wt／wt)である(1)から(4)いずれか記

載の経口製剤。

[12] ルラシドンの1錠中の含量が、10～160mgである請求項1～4いずれか記載の経口製剤。

[13] ルラシドンの1錠中の含量が、20～120mgである請求項1～4いずれか記載の経口製剤。

[14] ルラシドンの1錠中の含量が、40～120mgである請求項1～4いずれか記載の経口製剤。

[15] 水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[16] 水溶性賦形剤がマンニトールもしくは乳糖であり、製剤中のルラシドン含有量が25～40%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[17] アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[18] 水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して10～50%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[19] 水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)である請求項1～4いずれか記載の経口製剤。

[20] 水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)であり、ルラシドンの1錠中の含量が40～120mgである請求項1～4いずれか記載の経口製剤。

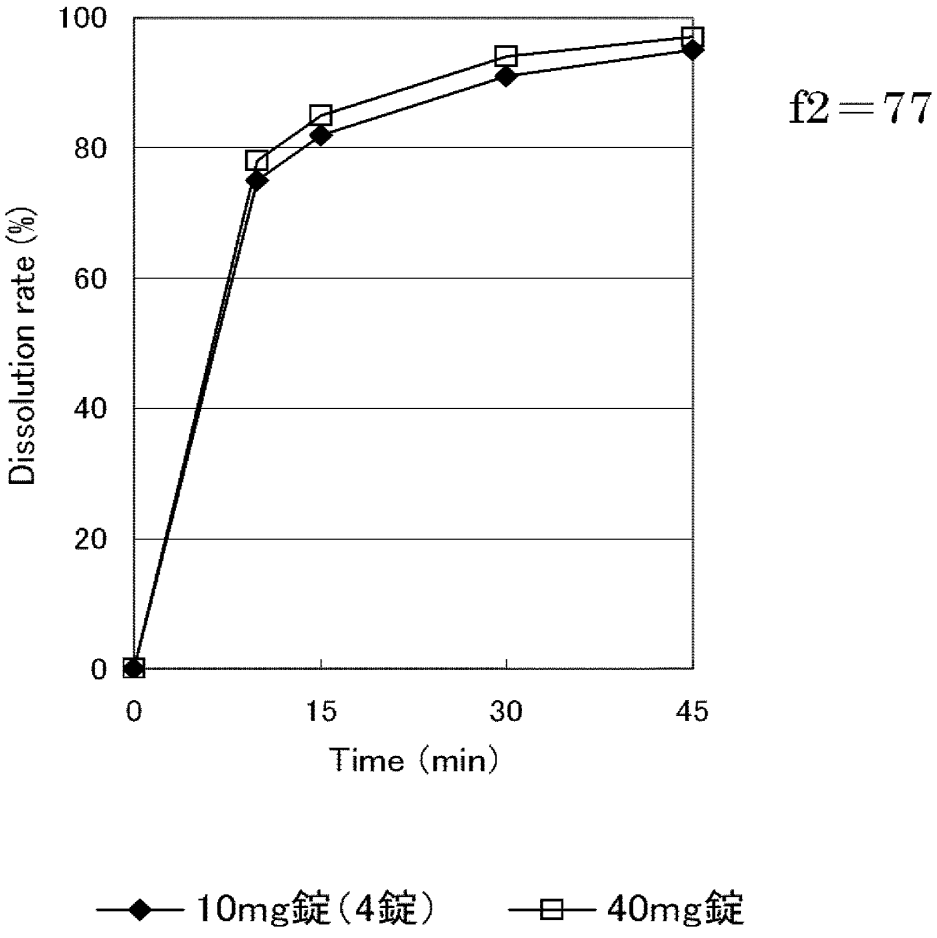
[21] アルファ化デンプン類のアルファ化率が50～95%である請求項1～4いずれか記載の経口製剤。

[22] ルラシドンの平均粒子径が0．1～8μmである請求項1～4いずれか記載の経口製剤。

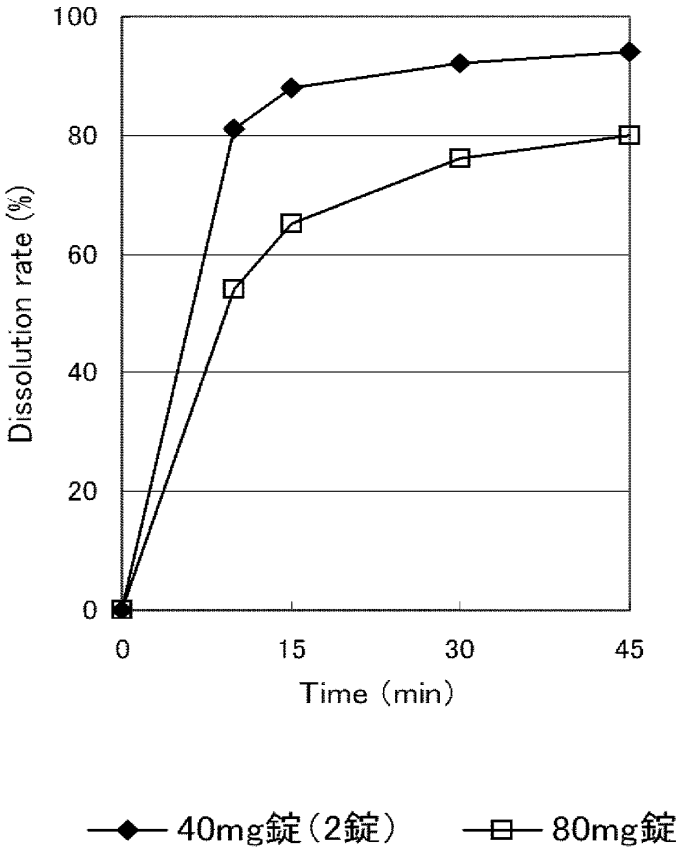
[23] アルファ化デンプン類中の水可溶分が、30%以下である請求項1～4いずれか記載の経口製剤

[24] 水溶性賦形剤がマンニトールもしくは乳糖であり、アルファ化デンプン類の配合量が製剤重量に対して20～30%(wt／wt)であり、製剤中のルラシドン含有量が25～40%(wt／wt)であり、ルラシドンの1錠中の含量が20～120 mg である請求項1～4いずれか記載の経口製剤。

[図1]

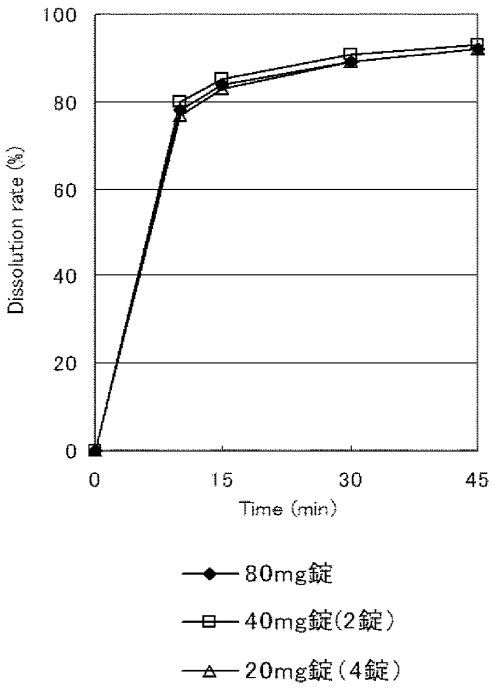

100
80
60
40
20
0
Dissolution rate (%)
0
15
30
45
Time (min)
f2＝77
10mg錠（4錠）
40mg錠

[図2]


100
80
60
40
20
0
Dissolution rate (%)
0
15
30
45
Time (min)
40mg錠(2錠)
80mg錠

$f2 = 37$

[図3]



f2＝88　(80 錠に対して 40mg 錠 2 錠)

f2＝97　(80 錠に対して 20mg 錠 4 錠)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/310571

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/496(2006.01), ***A61K9/20***(2006.01), ***A61K47/10***(2006.01), ***A61K47/26***(2006.01), ***A61K47/38***(2006.01), ***C07D417/12***(2006.01)

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)
A61K9/20, A61K31/496, A61K47/10, A61K47/26, A61K47/38, C07D417/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2006
Kokai Jitsuyo Shinan Koho 1971-2006 Toroku Jitsuyo Shinan Koho 1994-2006

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2002/024166 A1 (Sumitomo Pharmaceuticals Co., Ltd.), 28 March, 2002 (28.03.02), Full text; particularly, examples & AU 200186237 A & EP 1327440 A1 & US 2004/0028741 A1	1-24
A	WO 2004/078173 A1 (Shionogi & Co., Ltd.), 16 September, 2004 (16.09.04), Full text; particularly, Claim 3; example 7; Fig. 1 & TW 200423972 A	1-24
A	JP 08-325146 A (Kyowa Hakko Kogyo Co., Ltd.), 10 December, 1996 (10.12.96), Full text (Family: none)	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 August, 2006 (07.08.06)	15 August, 2006 (15.08.06)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (April 2005)

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ２００６／３１０５７１

Ａ．　発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int.Cl.　*A61K31/496* (2006.01), *A61K9/20* (2006.01), *A61K47/10* (2006.01), *A61K47/26* (2006.01), *A61K47/38* (2006.01), *C07D417/12* (2006.01)

Ｂ．　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int.Cl.　A61K 9/20, A61K 31/496, A61K 47/10, A61K 47/26, A61K 47/38, C07D 417/12

最小限資料以外の資料で調査を行った分野に含まれるもの

日本国実用新案公報	１９２２－１９９６年
日本国公開実用新案公報	１９７１－２００６年
日本国実用新案登録公報	１９９６－２００６年
日本国登録実用新案公報	１９９４－２００６年

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

REGISTRY(STN),CA(STN)

Ｃ．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	WO 2002/024166 A1（住友製薬株式会社）2002.03.28, 全文、特に、実施例参照　& AU 200186237 A & EP 1327440 A1 & US 2004/0028741 A1	1-24
A	WO 2004/078173 A1（塩野義製薬株式会社）2004.09.16, 全文、特に、請求項３、実施例７、図１参照　& TW 200423972 A	1-24

☑　Ｃ欄の続きにも文献が列挙されている。　　☐　パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「Ａ」特に関連のある文献ではなく、一般的技術水準を示すもの
「Ｅ」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「Ｌ」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「Ｏ」口頭による開示、使用、展示等に言及する文献
「Ｐ」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「Ｔ」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「Ｘ」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Ｙ」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「＆」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
０７．０８．２００６	１５．０８．２００６

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	４Ｃ	３７５５
日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	八原　由美子 電話番号　０３－３５８１－１１０１　内線　３４５２		

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（２００５年４月）

Ｃ（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	JP 08-325146 A（協和醗酵工業株式会社）1996.12.10, 全文参照,（ファミリーなし）	1-24

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/JP2006/310571

International filing date: 26 May 2006 (26.05.2006)

Document type: Certified copy of priority document

Document details: Country/Office: JP
Number: 2005-153508
Filing date: 26 May 2005 (26.05.2005)

Date of receipt at the International Bureau: 06 July 2006 (06.07.2006)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

日 本 国 特 許 庁
JAPAN PATENT OFFICE

別紙添付の書類に記載されている事項は下記の出願書類に記載されている事項と同一であることを証明する。

This is to certify that the annexed is a true copy of the following application as filed with this Office.

出 願 年 月 日 Date of Application:	２００５年　５月２６日
出 願 番 号 Application Number:	特願２００５－１５３５０８
パリ条約による外国への出願に用いる優先権の主張の基礎となる出願の国コードと出願番号 The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is	ＪＰ２００５－１５３５０８
出 願 人 Applicant(s):	大日本住友製薬株式会社

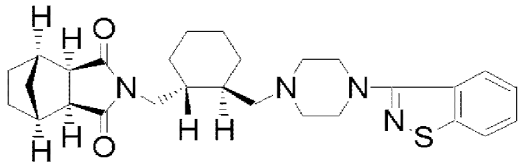
２００６年　６月２１日

特許庁長官
Commissioner,
Japan Patent Office

中 嶋 誠

【書類名】　特許願
【整理番号】　133348
【あて先】　特許庁長官殿
【国際特許分類】　A61K 31/495
【発明者】
　【住所又は居所】　大阪府茨木市蔵垣内１丁目３番４５号　住友製薬株式会社内
　【氏名】　富士原　和之
【特許出願人】
　【識別番号】　000183370
　【氏名又は名称】　住友製薬株式会社
【代理人】
　【識別番号】　100121588
　【弁理士】
　【氏名又は名称】　五十部　穣
　【電話番号】　06-6466-5214
【手数料の表示】
　【予納台帳番号】　056546
　【納付金額】　16,000円
【提出物件の目録】
　【物件名】　特許請求の範囲　1
　【物件名】　明細書　1
　【物件名】　図面　1
　【物件名】　要約書　1
　【包括委任状番号】　0205876

【書類名】特許請求の範囲
【請求項１】
式（１）
【化１】



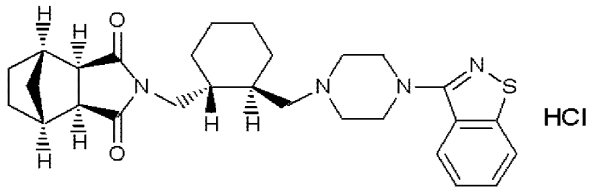
・HCl　(1)

で表されるＮ－[４－｛４－（１，２－ベンズイソチアゾール－３－イル）－１－ピペラジニル｝－（２Ｒ，３Ｒ）－２，３－テトラメチレン－ブチル]－（１'Ｒ，２'Ｓ，３'Ｒ，４'Ｓ）－２，３－ビシクロ｛２，２，１｝ヘプタンジカルボキシイミド・塩酸塩（ルラシドン・塩酸塩）、アルファ化デンプン類、水溶性賦形剤、水溶性高分子結合剤を含有する経口製剤。
【請求項２】
ルラシドン・塩酸塩、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いて造粒した経口製剤。
【請求項３】
アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン・塩酸塩及び水溶性高分子結合剤を溶解又は分散した液により、造粒した経口製剤。
【請求項４】
水溶性賦形剤がマンニトールもしくは乳糖である請求項１～３いずれか記載の経口製剤。
【請求項５】
ルラシドン・塩酸塩、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いることにより造粒する方法。
【請求項６】
アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン・塩酸塩及び水溶性高分子結合剤を溶解又は分散した液を用いることにより造粒する方法。
【請求項７】
水溶性賦形剤がマンニトールもしくは乳糖である請求項５記載の造粒方法。
【請求項８】
アルファ化デンプン類の配合量が製剤重量に対して１０～５０％（ｗｔ／ｗｔ）である請求項１から４記載の経口製剤。
【請求項９】
アルファ化デンプン類の配合量が製剤重量に対して２０～３０％（ｗｔ／ｗｔ）である請求項１から４記載の経口製剤。
【請求項１０】
製剤中のルラシドン・塩酸塩含有量が、２０～４０％（ｗｔ／ｗｔ）である請求項１から４いずれか記載の経口製剤。
【請求項１１】
ルラシドン・塩酸塩の１錠中の含量が、１０～１２０㎎である請求項１から４いずれか記載の経口製剤。
【請求項１２】
アルファ化デンプン類のアルファ化率が５０～９５％である請求項１から４いずれか記載の経口製剤。
【請求項１３】
ルラシドン・塩酸塩の平均粒子径が０．１～８μｍである請求項１から４いずれか記載の経口製剤。
【請求項１４】
アルファ化デンプン類中の水可溶分が、２０％以下である請求項１から４いずれか記載の

経口製剤

【書類名】明細書
【発明の名称】医薬品組成物
【技術分野】
【０００１】
本発明は、Ｎ－[４－〔４－(１，２－ベンズイソチアゾール－３－イル)－１－ピペラジニル〕－(２Ｒ，３Ｒ)－２，３－テトラメチレン－ブチル]－(１'Ｒ，２'Ｓ，３'Ｒ，４'Ｓ)－２，３－ビシクロ〔２，２，１〕ヘプタンジカルボキシイミド・塩酸塩（ルラシドン・塩酸塩）を有効成分とする崩壊性が良好な経口製剤に関する。詳しくはルラシドン・塩酸塩を有効成分とする経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤、特に錠剤に関する。
【背景技術】
【０００２】
特許文献１には、ルラシドン・塩酸塩等の化合物について、経口的に投与することができること、また通常の担体・賦形剤・結合剤・安定剤等と有効成分とを配合することにより製造できることの記載はあるが、該有効成分の含量が広い範囲で異なっても速溶解性を示し、かつ、同等の溶出挙動を示す経口用の製剤、とくに有効成分の含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示す経口製剤に関する記載はない。
【０００３】
含量が異なる製剤を同一用量服用したときの生物学的同等性を保証することを目的として医薬審第６４号(平成１２年２月１４日公布)にて『含量が異なる経口固形製剤の生物学的同等性試験ガイドライン』が示され、含量が異なる製剤において、胃、腸および口腔内の各ｐＨ値に対応するｐＨ１．２、３．０～５．０および６．８の緩衝液、水、生理食塩水などの各試験液で同等の溶出挙動を示すことが求められるようになった。
【０００４】
ルラシドン・塩酸塩を有効成分とする薬剤について、該有効成分の含量が異なっても速溶解性を示し、かつ、同等の溶出挙動を示す経口製剤、とくに有効成分の含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示し、水難溶性の有効成分を所望の濃度に放出し得る経口製剤については特許文献２に開示されている。
【０００５】
特許文献２には有効成分の含量が数ｍｇ～数十ｍｇの範囲、例えば５ｍｇ～２０ｍｇまたは５ｍｇ～４０ｍｇの範囲、で変動しても、速溶解性を示し、かつ、同一組成比において同等の溶出挙動を示す経口製剤、特に錠剤が開示されている。経口製剤においては、より高い臨床効果を得るためにさらに高い含量の製剤、又は患者の症状に応じて臨床効果を調節するためにより広い含量範囲で、複数錠と同様の挙動を示し、有効成分を所望の濃度に放出し得る製剤が必要とされる場合が多い。特許文献２の開示技術では図１に示すようにルラシドン・塩酸塩が１錠あたり５ｍｇから４０ｍｇまでは同等の溶出挙動を示す経口製剤を提供することができる。しかしながら、図２に示すように、製剤中の有効成分の含有率を２倍にすることにより一錠中の有効成分の含有量を増やした場合、８０ｍｇ錠では同等の溶出挙動を示すことができなかった。従って、複数錠を一度に服用するか、服用に困難な大きさの錠剤にせざるを得ない状況であった。よって、水難溶性の有効成分であるルラシドン・塩酸塩については、高含量の経口製剤あるいはさらに広い範囲で溶出挙動が同等な経口製剤の提供は困難であった。
【０００６】
また、特許文献２には水溶性高分子結合剤としてデンプンが挙げられているが、アルファ化デンプンについての記載はない。アルファ化デンプンは、例えば、特許文献３に記載されているように、医薬品組成物の崩壊性及び溶出性が顕著に改善することが知られているが、医薬品に採用されることは必ずしも多くはない。崩壊剤として使用される場合、非特許文献１の中でも記述されるように通常、１０％以下の含有量で用いられることが多い。
【０００７】

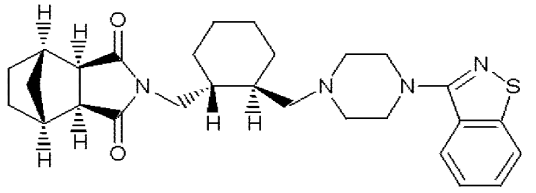
【特許文献１】特許第２８００９５３
【特許文献２】ＷＯ２００２／０２４１６６
【特許文献３】特開２０００－２６２９２
【非特許文献１】Handbook of Pharmaceutical Excipients，2nd edition，491，1994，The Pharmaceutical Press
【発明の開示】
【発明が解決しようとする課題】
【０００８】
本発明の目的は、ルラシドン・塩酸塩を有効成分とし、該有効成分の含量が広い範囲で異なっても速溶解性を示し、かつ、同等の溶出挙動を示す経口用の製剤、とくに有効成分の含量を増大した場合に低含量の製剤の複数錠と同様の溶出挙動を示し、有効成分を所望の濃度に放出し得る経口製剤を提供することにある。
【０００９】
Ｎ－[４－｛４－(１，２－ベンズイソチアゾール－３－イル)－１－ピペラジニル｝－(２Ｒ，３Ｒ)－２，３－テトラメチレン－ブチル]－(１'Ｒ，２'Ｓ，３'Ｒ，４'Ｓ)－２，３－ビシクロ｛２，２，１｝ヘプタンジカルボキシイミド・塩酸塩（以下、ルラシドン・塩酸塩）を有効成分とする経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤の提供することを目的とする。
【課題を解決するための手段】
【００１０】
本発明者らは、前記課題を解決するために鋭意検討したところ、以下の手段により当該課題を解決することを見いだすに至った。
【００１１】
すなわち、本発明は、以下の通りである。
（１）式（１）
【００１２】
【化１】



(1)

で表されるＮ－[４－｛４－(１，２－ベンズイソチアゾール－３－イル)－１－ピペラジニル｝－(２Ｒ，３Ｒ)－２，３－テトラメチレン－ブチル]－(１'Ｒ，２'Ｓ，３'Ｒ，４'Ｓ)－２，３－ビシクロ｛２，２，１｝ヘプタンジカルボキシイミド・塩酸塩（ルラシドン・塩酸塩）、アルファ化デンプン類、水溶性賦形剤、水溶性高分子結合剤を含有する経口製剤。
（２）ルラシドン・塩酸塩、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いて造粒した経口製剤。
（３）アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン・塩酸塩及び水溶性高分子結合剤を溶解又は分散した液により、造粒した経口製剤。
（４）水溶性賦形剤がマンニトールもしくは乳糖である（１）～（３）いずれか記載の経口製剤。
（５）ルラシドン・塩酸塩、アルファ化デンプン類及び水溶性賦形剤を含む混合末を、水溶性高分子結合剤を溶解した溶液を用いることにより造粒する方法。
（６）アルファ化デンプン類及び水溶性賦形剤を含む混合末を、ルラシドン・塩酸塩及び水溶性高分子結合剤を溶解又は分散した液を用いることにより造粒する方法。
（７）水溶性賦形剤がマンニトールもしくは乳糖である（５）記載の造粒方法。
（８）アルファ化デンプン類の配合量が製剤重量に対して１０～５０％（ｗｔ／ｗｔ）である（１）から（４）いずれか記載の経口製剤。

（９）アルファ化デンプン類の配合量が製剤重量に対して２０～３０％（ｗｔ／ｗｔ）である（１）から（４）いずれか記載の経口製剤。
（１０）製剤中のルラシドン・塩酸塩含有量が、２０～４０％（ｗｔ／ｗｔ）である（１）から（４）いずれか記載の経口製剤。
（１１）ルラシドン・塩酸塩の１錠中の含量が、１０～１２０mgである（１）から（４）いずれか記載の経口製剤。
（１２）アルファ化デンプン類のアルファ化率が５０～９５％である（１）から（４）いずれか記載の経口製剤。
（１３）ルラシドン・塩酸塩の平均粒子径が０．１～８μｍである（１）から（４）いずれか記載の経口製剤。
（１４）アルファ化デンプン類中の水可溶分が、２０％以下である（１）から（４）いずれか記載の経口製剤
【発明の効果】
【００１３】
本発明によりルラシドン・塩酸塩を有効成分とする崩壊性が良好な経口製剤において、ルラシドン・塩酸塩を高含有量含む経口製剤の提供が、また有効成分の含量が変動しても同等の溶出挙動を示す経口投与用製剤を提供することが可能となった。また、配合変化を起こさず、長期保存性にも優れている。
【発明を実施するための最良の形態】
【００１４】
Ｎ－[４－〔４－(１，２－ベンズイソチアゾール－３－イル)－１－ピペラジニル〕－(２Ｒ，３Ｒ)－２，３－テトラメチレン－ブチル]－(１'Ｒ，２'Ｓ，３'Ｒ，４'Ｓ)－２，３－ビシクロ〔２，２，１〕ヘプタンジカルボキシイミド・塩酸塩（ルラシドン・塩酸塩）は下記式：
【００１５】
【化２】



(1)

で示される化合物である(特許第２８００９５３号参照)。ルラシドン・塩酸塩は向精神病作用を持つことが知られており、統合失調症等の治療薬として有効である。本化合物の配合量としては、錠剤全重量に基づいて、例えば、１０～５０重量％の範囲、好ましくは２０～４０重量％の範囲から選択される。更に、微粉砕されていることが好ましく、例えば体積比９０％以上の粒子が２７μｍ以下であり、体積比による平均粒子径としては例えば、０．１～８μｍの範囲が挙げられる。好ましくは、１～６μｍの範囲が挙げられる。１錠中に含まれるルラシドン・塩酸塩の含量としては、１０－１２０ｍｇ、好ましくは２０－８０ｍｇが挙げられる。
【００１６】
「アルファ化デンプン類」とは例えばトウモロコシデンプン、バレイショデンプン、コムギデンプン、コメデンプン、タピオカデンプン等各種デンプン類をアルファ化したものであり、このようなものとしては例えば医薬品添加物規格にあるアルファ化デンプン（英語名：Pregelatinized Starch）又は部分アルファ化デンプン（英語名：Partly Pregelatinized Starch）等を挙げることができる。アルファ化デンプン類のアルファ化率は、例えば５０～１００％、好ましくは５０～９５％、さらに好ましくは８０～９５％である。更に、アルファ化デンプン類中の水可溶分は、例えば２０％以下、より好ましくは５％以下である。これらアルファ化デンプン類は、通常、平均粒径が１～１０００μｍ、好ましくは１～５００μｍ、さらに好ましくは１０～１００μｍの粉末が用いられる。本発明に

適する市販のアルファ化デンプン類としては、例えばＰＣＳ（商品名、旭化成工業株式会社製）又はスターチ１５００（商品名、カラコン）等の部分アルファ化デンプンが挙げられる。上記アルファ化デンプン類の中でも部分アルファ化デンプン、例えばＰＣＳ（商品名、旭化成工業株式会社製）が好ましく用いられる。部分アルファ化デンプンのアルファ化率は、好ましくは５０～９５％、さらに好ましくは８０～９５％である。本発明において用いられるアルファ化デンプン類は、製剤重量に対して１０％以上５０％以下であり、好ましくは１０％以上３０％以下であり、特に好ましくは、２０％以上３０％以下である。

【００１７】

「水溶性賦形剤」としては、例えばマンニトール、乳糖、白糖、ソルビトール、Ｄ－ソルビトール、エリスリトール、キシリトール等が挙げられる。より好ましいものとしてはマンニトール及び乳糖が挙げられる。さらに好ましくはマンニトールを挙げることができる。また、該水溶性賦形剤は、１種または同時に２種以上を使用することができる。水溶性賦形剤の配合量としては、錠剤全重量に基づいて、例えば、３０～８０重量％の範囲、好ましくは４０～６０重量％の範囲から選択される。また、マンニトールの平均粒子径としては、例えば１０～２００μｍの範囲が挙げられる。

【００１８】

「水溶性高分子結合剤」としては、例えば、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン、ポリビニルアルコール等が挙げられる。より好ましいものとしては、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン、ポリビニルアルコールが挙げられる。該水溶性高分子結合剤は、これらの１種または同時に２種類以上を用いることができる。水溶性高分子結合剤の配合量としては錠剤全重量に基づいて、例えば、０．５～１０重量％の範囲、好ましくは１～５重量％の範囲から選択される。

本発明の医薬品組成物から成る経口製剤は、錠剤、カプセル剤、顆粒剤、細粒剤に製剤化されるものをいう。慣用手段によって、水溶性賦形剤に加えて非水溶性賦形剤、結合剤、崩壊剤、滑沢剤、等を使用して、錠剤、カプセル剤、顆粒剤、細粒剤に製剤化されるものであってもよい。また、以下のものを加えることもできる。

【００１９】

「非水溶性賦形剤」としては、例えばコーンスターチ、結晶セルロース等が挙げられる。また、１種または同時に２種以上を使用することができる。

【００２０】

「崩壊剤」としては、例えば、コーンスターチ、結晶セルロース、低置換度ヒドロキシプロピルセルロース、カルメロース、カルメロースカルシウム、カルメロースナトリウム、クロスカルメロースナトリウム、カルボキシメチルスターチナトリウム、クロスポビドン等が挙げられる。該崩壊剤は、１種または同時に２種以上を使用することができる。該崩壊剤の平均粒子径としては、例えば、５～７５μｍの範囲のものが挙げられ、好ましくは５～７５μｍの範囲の平均粒子径を有し、７５μｍを越える粒子が全体の５％以下であることが望ましい。崩壊剤の配合量としては、錠剤全重量に基づいて、例えば、０～１０重量％の範囲、好ましくは０．５～５重量％の範囲が挙げられる。

【００２１】

「滑沢剤」としては、例えばステアリン酸マグネシウム、タルク、ポリエチレングリコール、シリカ、硬化植物油等が挙げられる。

【００２２】

本発明の経口製剤の調製は、所望の剤形により異なるが、常法にしたがって所望の剤形にすることができる。

（１）水溶性高分子結合剤の水溶液の調製：

水溶性高分子結合剤を精製水に溶解する。その際の温度としては、例えば、２０℃から９０℃の範囲から選択され、好ましくは、２０℃から７０℃の範囲から選択される。水溶性高分子結合剤の量としては、精製水の量に対し、例えば１～２０重量％の範囲、好まし

くは２～８重量％の範囲から選択される。
(２)ルラシドン・塩酸塩含有造粒物の調製：
ルラシドン・塩酸塩、マンニトール、部分アルファ化デンプンを含む賦形剤および崩壊剤を仕込んだ流動層造粒機に、上記(１)の工程で調製された水溶性高分子結合剤を散布しながら造粒する。

【００２３】
造粒装置としては、例えば、流動層造粒(Fluid Bed Granulation)、高速攪拌造粒(High share granulation)、転動型流動層造粒(Roto Fluid Bed Granulation)等に分類される造粒装置が挙げられる。但し、これらに限定されるものではない。
（３）造粒物の乾燥：
上記造粒物を、減圧または常圧にて乾燥する。この乾燥は、赤外線水分計にて測定される乾燥減量値が、例えば、３重量％以内、好ましくは１～２重量％以内になるように行う。
（４）滑沢剤の配合：
上記(３)で乾燥した造粒物に滑沢剤を加えて混合する。混合は、例えば、攪拌ミキサー[タンブル](Diffusion mixers [Tumble])に分類される混合機が用いられる。具体的には、タンブラーブレンダー(Tumble Blender)、Ｖブレンダー(V Blenders)、ダブルコーン(Double Cone)、ビンタンブラー(Bin Tumble)等が挙げられる。但し、これらに限定されるものではない。
(５)打錠：
上記混合物を打錠して錠剤を調製する。
【００２４】
打錠装置としては、例えば、錠剤プレス(Tablet Press)に分類される打錠機等が挙げられる。打錠硬度としては、例えば３０～２００Ｎ範囲から選択される。
(６)所望によりフィルムコーティングを施す：
上記錠剤には、必要に応じてフィルムコーティングしてもよい。コーティング装置としては、例えばコーティングパンに分類される装置が挙げられる。好ましくは、通気式コーティングシステム(Perforated Coating System)で分類される装置が挙げられる。
【００２５】
コーティング剤としては、例えば、ヒドロキシプロピルメチルセルロース、ヒドロキシプロピルセルロース、ポリビニルピロリドン、ポリビニルアルコール等の基剤と、例えば、ポリエチレングリコール、プロピレングリコール、トリアセチン、クエン酸トリエチル、グリセリン、グリセリン脂肪酸エステル、ポリエチレングリコール等の可塑剤を組み合わせたものが挙げられる。また、必要に応じて、酸化チタン等の添加剤を加え調製することもできる。また、フィルムコーティング後に、光沢化剤としてカルナバロウ等を加えることもできる。
(７)乾燥：
上記のようにして得られた錠剤を乾燥する。乾燥は減圧または常圧で行い、赤外線水分計にて測定される乾燥減量値が、例えば、３重量％以内、好ましくは１～２重量％以内になるように行う。
【００２６】
以下に本発明の実施例を挙げるが、本実施例は本発明を説明するためのものであって、本発明をなんら限定するものではない。
【実施例１】
【００２７】
Ａ．ルラシドン・塩酸塩を８０ｍｇ含有するフィルムコート錠（実施例１）
下記組成からなる顆粒、裸錠およびＦＣ錠を順次調製する。尚、説明文中の括弧内に示す仕込み量は実施例１に示す処方の製剤を調製するための一例を示すものである。
原則としてこの製造方法に準じれば、その他に示す実施例についても調製できる。但し、

仕込み量は処方に基づき変更する必要がある。
【００２８】
Ｂ．製造方法
(１)結合液の調製（５％　ヒドロキシプロピルメチルセルロース水溶液）：
水溶性高分子結合剤のヒドロキシプロピルメチルセルロース(３２ｇ)を精製水(６４０ｇ)に溶解し、これを結合液とした。
(２)造粒：
ルラシドン・塩酸塩（３２０ｇ）、マンニトール(５７６ｇ)、部分アルファ化デンプン（３２０ｇ）、クロスカルメロースナトリウム(１６ｇ)を流動層造粒機(マルチプレックスＭＰ－０１／パウレック製)に仕込み、上記(１)で調製した結合液を用いて、下記条件でスプレー造粒し造粒末を得た。得られた造粒末にステアリン酸マグネシウムを加えて混合後(４０ｒｐｍ、５分)に、処方(ｂ)を有する打錠用顆粒を得た。尚、ステアリン酸マグネシウムの仕込み量は造粒末の収量に基づき処方から算出される量を混合した。
造粒条件
給気温度：６０℃
風量：５０－６５m^3／ｈｒ
スプレー速度：１３ｇ／分
スプレーノズル径：１．２ｍｍ
スプレー圧力：０．１２ＭＰａ
ガン位置：中段
(３)打錠：
上記(２)で調製した打錠用顆粒をHT-AP12SS-II(畑鉄工所)を用いて錠剤を成形した。
杵サイズ：φ１０ｍｍ１４Ｒ
厚み：４．２０～４．３０ｍｍ
打錠圧縮圧力：１０ＫＮ
(４)コーティング：
上記(３)で調製した裸錠をハイコーターＨＣＴ３０Ｎ(フロイント産業)で皮膜量が５ｍｇになるように下記条件でコーティングを行い、コーティング後にカルナバロウを添加しフィルムコート錠を得た。
ＦＣ条件
給気温度　：８０℃
風量　　：０．６m^3／分
パン回転数：２５ｒｐｍ
スプレー圧：０．１５ＭＰａ
液速　　：５ｇ／分
上述の方法により得られた製剤は以下の方法により品質を評価し、そこで得られた知見をもとに本発明を見出すに至った。
【００２９】
Ｃ．品質評価
（１）溶出試験
日本薬局方溶出試験法第２法に従い、試作した製剤の溶出試験を実施した。以下に測定条件を示す。
試験溶液：希釈マックイルベイン緩衝液(diluted McIlvaine buffer、ｐＨ４．０)
パドル回転数：５０ｒｐｍ
試験液：９００ｍｌ
（２）溶出プロファイルの類似性
溶出プロファイルの類似性を評価するための指標としてScale-Up and Past-Approval Changes for Intermediate Release Products(SUPAC-IR)に示される類似因子f2を用いた。f2は以下の式により算出される。SUPAC-IRにより各製剤の溶出率から算出されるf2値が５０≦f2≦１００の範囲にある場合、試作した各製剤は類似の溶出プロファイルであると判

定した。また、f2値の算出に当っては試験開始後１５分、３０分および４５分の３ポイントの時点での溶出率を用いた。

【００３０】

【数１】

$$f2 = 50 \cdot LOG\left[\frac{100}{\sqrt{1 + \frac{\sum_{i=1}^{n}(Ti - Ri)^2}{n}}}\right]$$

Ti and Ri are the percent dissolved at each point.
n is the number of points to be compared.

（３）粒度分布

レーザー回折粒度分布測定装置（SLAD-3000/島津製作所）の乾式噴射法にてルラシドン・塩酸塩の粒度分布を測定した。以下に測定条件を示す。

試料量：2g
エアー圧：0.4MPa以上
ターンテーブル回転スピード：2
パラメータ設定
環境設定
モニター平均回数：16　　測定最適範囲（最大）　：1500
暗測定平均回数　：2　　（最小）　：700
光強度表示最大値：2000　　(CH-1) ボーレート(bps)：9600
前回のブランク値：読み込み　　ブランク測定許容最大値　：300
プリンター：モノクロ　　ブランク測定許容変動範囲：20
屈折率パラメーター
標準屈折率：1.70-0.20i
測定条件設定
測定回数：1　　乾式許容最小値：300
測定間隔（秒）：1　　最大値：2500
平均回数：64　　評価対象粒子範囲（最小値）：0.1
測定吸光度範囲（最大値）：0.1　　評価対象粒子範囲（最大値）：2000
（最小値）：0.05　センサ使用開始位置：1
トリガーモード：OFF
乾式しきい：300

【００３１】

＜試験１＞

実施例１、２，３で、１錠中にルラシドン・塩酸塩を２０ｍｇ、４０ｍｇおよび８０ｍｇ含有する水溶性賦形剤、部分アルファ化デンプンおよび水溶性高分子結合剤から成る特定の医薬品組成物を含む錠剤を試作した。また、比較例１、２で、特許文献２の開示処方に基づき１錠中にルラシドン・塩酸塩を４０ｍｇおよび８０ｍｇ含有する錠剤を試作した。

試作した製剤を（ｄ）および（ｅ）に示す条件で溶出試験を実施し、溶出プロファイルの類似性を評価した。なお、比較例１、２の試作については試験８にて示した。

結果は、表４，５に示した。なお、（ｄ）については経時的な溶出率についても図２，３で示した。

【００３２】

（ａ）造粒末の処方

【００３３】

【表１】

単位：ｍｇ

成分	実施例番号			比較例番号	
	1	2	3	1	2
ルラシドン・塩酸塩	80	40	20	40	80
マンニトール	144	72	36	188	148
部分アルファ化デンプン	80	40	20	−	−
クロスカルメロースナトリウム	4	2	1	16	16
ヒドロキシプロピルメチルセルロース	8	4	2	10	10

【００３４】

（ｂ）打錠用顆粒/裸錠の処方

【００３５】

【表２】

単位：ｍｇ

成分	実施例番号			比較例番号	
	1	1	1	1	2
上記（ａ）の顆粒	316	158	79	254	254
乳糖	−	−	−	62	62
ステアリン酸マグネシム	4	2	1	4	4

【００３６】

（ｃ）ＦＣ錠の処方

【００３７】

【表３】

単位：ｍｇ

成分	実施例番号			比較例番号	
	1	2	3	1	2
上記(ｂ)の裸錠	320	160	80	320	320
ヒドロキシプロピルメチルセルロース	3.25	1.95	1.3	2.6	2.6
酸化チタン	1	0.6	0.4	0.8	0.8
ポリエチレングリコール６０００	0.75	0.45	0.3	0.6	0.6
カルナバロウ	0.01	0.006	0.004	0.01	0.01

【００３８】

（ｄ）１ベッセル当りルラシドン・塩酸塩が８０ｍｇとなる系での溶出試験

１ベッセル当りルラシドン・塩酸塩が８０ｍｇとなる系でルラシドン・塩酸塩を８０ｍｇ、４０ｍｇおよび２０ｍｇを含有する各フィルムコート錠の溶出試験を実施し、それぞれの溶出プロファイルの類似性をｆ２値により評価した。

【００３９】

表４から明らかなように、実施例２，３のｆ２値は実施例1に対する類似性を示したが、比較例２のｆ２値は比較例1に対する類似性を示さなかった。即ち、表４，図３から明らかなように、実施例１乃至３は溶出プロファイルの類似性を示すｆ２値が５０≦ｆ２≦１００の範囲となり、含量の異なる製剤においても、錠剤の含量（力価）に依存することなく溶出プロファイルの類似性を示す製剤が得られた。一方、表４，図２から明らかにように、詳細を試験８に記載したが、特許文献２開示処方の比較例２は比較例１からなる製剤２錠の溶出よりも明らかに遅く、溶出プロファイルの類似性は示さなかった。

【００４０】

【表４】

類似因子	実施例番号			比較例番号	
	1	2	3	1	2
ｆ２	－	８８	９７	－	３７

【００４１】
（ｅ）１ベッセル当りルラシドン・塩酸塩が４０ｍｇとなる系での溶出試験
１ベッセル当りルラシドン・塩酸塩が４０ｍｇとなる系でルラシドン・塩酸塩を４０ｍｇおよび２０ｍｇを含有する各フィルムコート錠の溶出試験を実施し、それぞれの溶出プロファイルの類似性を同様にｆ２値を用いて評価した。
【００４２】
表５から明らかなように、実施例３，比較例１のｆ２値は実施例２に対する類似性を示した。即ち、１ベッセル当りルラシドン・塩酸塩が４０ｍｇである系においても、ｆ２値は５０≦ｆ２≦１００の範囲となり、錠剤の含量（力価）に依存することなく溶出プロファイルの類似性が示された。
【００４３】
【表５】

類似因子	実施例番号		比較例番号
	2	3	1
ｆ２	－	８８	９７

【００４４】
＜試験２＞
実施例１および４で、水溶性賦形剤と水溶性高分子結合剤および部分アルファ化デンプンから成る医薬品組成物を含む製剤を調製した。また、比較例３，４および５で、水溶性賦形剤と水溶性高分子結合剤およびアルファ化していないデンプンであるコーンスターチから成る医薬品組成物を含む製剤を調製した。各製剤の溶出試験を実施し、溶出プロファイルの類似性をｆ２値により評価した。結果は、表９に示した。
（ａ）造粒末の処方
【００４５】
【表６】

単位：ｍｇ

成分	実施例番号		比較例番号		
	1	4	3	4	5
ルラシドン・塩酸塩	80	80	80	80	80
マンニトール	144	176	108	108	–
乳糖	–	–	–	–	108
部分アルファ化デンプン	80	40	–	–	–
コーンスターチ	–	–	40	40	40
クロスカルメロースナトリウム	4	8	16	16	16
ヒドロキシプロピルメチルセルロース	8	12	10	10	10

【００４６】
（ｂ）打錠用顆粒/裸錠の処方
【００４７】

【表７】

単位：ｍｇ

成分	実施例番号		比較例番号		
	1	4	3	4	5
上記（ａ）の顆粒	316	316	254	254	254
マンニトール	－	－	62	－	－
ステアリン酸マグネシム	4	4	4	4	4

【００４８】

（ｃ）ＦＣ錠の処方

【００４９】

【表８】

単位：ｍｇ

成分	実施例番号		比較例番号		
	1	4	3	4	5
上記(ｂ)の裸錠	320	320	320	258	258
ヒドロキシプロピルメチルセルロース	3.25	－	2.6	2.6	2.6
酸化チタン	1	－	0.8	0.8	0.8
ポリエチレングリコール６０００	0.75	－	0.6	0.6	0.6

【００５０】

（ｄ）溶出試験

表９から明らかなように、実施例４は実施例１に対する類似性を示したが、比較例３、４、５のｆ２値は実施例１に対して類似性を示さなかった。即ち、比較例３，４および５のコーンスターチを含む製剤は、実施例１および４の部分アルファ化デンプンを含む製剤と比較して、溶出プロファイルが異なり、溶出の遅い製剤であった。

【００５１】

【表９】

類似因子	実施例番号		比較例番号		
	1	4	3	4	5
ｆ２	－	６７	４４	２９	２６

【００５２】

＜試験３＞

実施例４，５，６，７で、部分アルファ化デンプンの配合量の溶出性に及ぼす影響を評価した。結果は表１３に示した。

（ａ）造粒末の処方

【００５３】

【表１０】

単位：ｍｇ

成分	実施例番号				
	1	4	5	6	7
ルラシドン・塩酸塩	80	80	80	80	80
マンニトール	144	176	116	136	156
部分アルファ化デンプン	80	40	100	80	60
クロスカルメロースナトリウム	4	8	8	8	8
ヒドロキシプロピルメチルセルロース	8	12	12	12	12

【００５４】

（ｂ）打錠用顆粒/裸錠の処方

【００５５】
【表１１】

単位：ｍｇ

成分	実施例番号				
	1	4	5	6	7
上記（ａ）の顆粒	316	316	316	316	316
ステアリン酸マグネシム	4	4	4	4	4

【００５６】
（ｃ）ＦＣ錠の処方
【００５７】
【表１２】

単位：ｍｇ

成分	実施例番号				
	1	4	5	6	7
上記(ｂ)の裸錠	320	320	320	320	320
ヒドロキシプロピルメチルセルロース	3.25	−	−	−	−
酸化チタン	1	−	−	−	−
ポリエチレングリコール６０００	0.75	−	−	−	−
カルナバロウ	0.01	−	−	−	−

【００５８】
（ｄ）溶出試験
表１３から明らかなように、実施例４、５、６、７のｆ２値は実施例１に対する類似性を示した。即ち、部分アルファ化デンプンを製剤組成中の１０％wt/wt以上含有する医薬品組成物から成る製剤は、速溶解性を示し、かつ、類似の溶出プロファイルを示した。
【００５９】
【表１３】

類似因子	実施例番号				
	1	4	5	6	7
ｆ２	−	６７	６０	６２	８１

【００６０】
＜試験４＞
比較例６で、水溶性賦形剤と部分アルファ化デンプンを含むが、水溶性高分子結合剤を含まない錠剤の製剤化を試みたが、打錠工程において、キャッピングとスティッキングが発生し打錠できず、類似の溶出プロファイルを得るどころか錠剤すら得られなかった。実施例８，９，１０および１１で、水溶性賦形剤および部分アルファ化デンプンと水溶性高分子結合剤の配合量の異なる医薬品組成物を含む製剤を調製した。結果は、表１７に示した。
（ａ）造粒末の処方
【００６１】

【表１４】

単位：ｍｇ

成分	実施例番号				比較例番号	
	1	8	9	10	11	6
ルラシドン・塩酸塩	80	80	80	80	80	80
マンニトール	144	136	138	140	142	148
部分アルファ化デンプン	80	80	80	80	80	80
クロスカルメロースナトリウム	4	8	8	8	8	8
ヒドロキシプロピルメチルセルロース	8	12	10	8	6	−

【００６２】

（ｂ）打錠用顆粒/裸錠の処方

【００６３】

【表１５】

単位：ｍｇ

成分	実施例番号					比較例番号
	1	8	9	10	11	6
上記（ａ）の顆粒	316	316	316	316	316	316
ステアリン酸マグネシム	4	4	4	4	4	4

【００６４】

（ｃ）ＦＣ錠の処方

【００６５】

【表１６】

単位：ｍｇ

成分	実施例番号					比較例番号
	1	8	9	10	11	6
上記(ｂ)の裸錠	320	320	320	320	320	320
ヒドロキシプロピルメチルセルロース	3.25	−	−	−	−	−
酸化チタン	1	−	−	−	−	−
ポリエチレングリコール６０００	0.75	−	−	−	−	−
カルナバロウ	0.01	−	−	−	−	−

【００６６】

（ｄ）溶出試験

表１７から明らかなように、実施例８，９、１０、１１のｆ２値は実施例1に対する類似性を示した。即ち、水溶性高分子結合剤を１．８％wt/wtから３．８％wt/wtの範囲において含有する医薬品組成物から成る製剤は、速溶解性を示し、かつ、類似の溶出プロファイルを示した。

【００６７】

【表１７】

類似因子	実施例番号				
	1	8	9	10	11
ｆ２	−	７７	８１	７３	７３

【００６８】

＜試験５＞

実施例１２で、水溶性賦形剤として乳糖を用い、水溶性高分子結合剤および部分カルファー化デンプンから成る医薬品組成物を含む製剤を調製した。結果は、表２１に示した。

（ａ）造粒末の処方

【００６９】
【表１８】

単位：ｍｇ

成分	実施例番号		
	1	6	12
ルラシドン・塩酸塩	80	80	80
マンニトール	144	136	–
乳糖	–	–	136
部分アルファ化デンプン	80	80	80
クロスカルメロースナトリウム	4	8	8
ヒドロキシプロピルメチルセルロース	8	12	12

【００７０】
（ｂ）打錠用顆粒/裸錠の処方
【００７１】
【表１９】

単位：ｍｇ

成分	実施例番号		
	1	6	12
上記（ａ）の顆粒	316	316	316
ステアリン酸マグネシム	4	4	4

【００７２】
（ｃ）ＦＣ錠の処方
【００７３】
【表２０】

単位：ｍｇ

成分	実施例番号		
	1	6	12
上記(ｂ)の裸錠	320	320	320
ヒドロキシプロピルメチルセルロース	3.25	–	–
酸化チタン	1	–	–
ポリエチレングリコール６０００	0.75	–	–
カルナバロウ	0.01	–	–

【００７４】
（ｄ）溶出試験
表２１から明らかなように、実施例６および１２のｆ２値は実施例１に対する類似性を示した。即ち、水溶性賦形剤としてマンニトールおよび乳糖にて速溶解性を示し、かつ、類似の溶出プロファイルを示した。
【００７５】
【表２１】

類似因子	実施例番号		
	1	6	12
ｆ２	—	６２	６６

【００７６】
＜試験６＞
実施例４，１３，１４および１５で、粒度分布の異なるルラシドン・塩酸塩原末を用いて、水溶性賦形剤と水溶性高分子結合剤および部分アルファ化デンプンから成る特定の医

薬品組成物を含む製剤を調製した。結果は、表２５に示した。
（ａ）ルラシドン・塩酸塩原末の粒度分布
D50 %（５０％粒子径）とは体積基準により算出される積算分布が５０％となるポイントでの粒子径を示し、D90 %（９０％粒子径）とは、体積基準により算出される積算分布が９０％（ふるい下）となるポイントでの粒子径を表す。
【００７７】
【表２２】

単位：ｍｇ

粒度分布		実施例番号			
		4	13	14	15
粒子径	D10 %	0.5	0.9	1.0	1.5
	D50 %	1.6	5.9	7.6	13.9
	D90 %	4.7	17.5	26.9	58.3

【００７８】
（ｂ）打錠用顆粒/裸錠の処方
【００７９】
【表２３】

単位：ｍｇ

成分	実施例番号			
	4	13	14	15
ルラシドン・塩酸塩	80	80	80	80
マンニトール	176	144	144	144
部分アルファ化デンプン	40	80	80	80
クロスカルメロースナトリウム	8	4	4	4
ヒドロキシプロピルメチルセルロース	12	8	8	8
ステアリン酸マグネシウム	4	4	4	4

【００８０】
（ｃ）ＦＣ錠の処方
【００８１】
【表２４】

単位：ｍｇ

成分	実施例番号			
	4	13	14	15
上記(ｂ)の裸錠	320	320	320	320
ヒドロキシプロピルメチルセルロース	-	3.25	3.25	3.25
酸化チタン	-	1	1	1
ポリエチレングリコール６０００	-	0.75	0.75	0.75
カルナバロウ	-	0.01	0.01	0.01

【００８２】
（ｄ）溶出試験
表２５から明らかなように、実施例１３，１４、１５のｆ２値は実施例４に対する類似性を示した。即ち、５０％粒子径が１～８μｍの範囲、９０％粒子径が２７μｍ以下の粒度分布のルラシドン・塩酸塩原末を用いて調製した製剤で類似の溶出プロファイルが得られることを見出した。
【００８３】

【表２５】

類似因子	実施例番号			
	4	13	14	15
ｆ２	－	５６	５６	４６

【００８４】

＜試験７＞

特許文献２の開示技術を用いて１錠中のルラシドン・塩酸塩の含有量が１０ｍｇと４０ｍｇとなる製剤を試作し、開示文献２の通り、１錠中のルラシドン・塩酸塩含量が１０ｍｇから４０ｍｇまでは同等の溶出挙動を示す経口製剤を提供できるかどうか検証した。結果は、図１に示した。

【００８５】

図１から明らかなように、特許文献２の開示技術により得られるルラシドン・塩酸塩を異なる含有量を有する製剤の溶出プロファイルは、ｆ２の値から明らかなように、１錠中にルラシドン・塩酸塩を１０ｍｇ含有する錠剤と４０ｍｇ含有する製剤は、特許文献２のとおり同等の溶出挙動を示す経口製剤を提供できた。

（ａ）顆粒の処方

単位：ｍｇ

成分	10mg錠	40mg錠
ルラシドン・塩酸塩	10	40
マンニトール	47	188
クロスカルメロースナトリウム	4	16
ヒドロキシプロピルメチルセルロース	2.5	10

【００８６】

（ｂ）裸錠の処方

c

単位：ｍｇ

成分	10mg錠	40mg錠
（ａ）の顆粒	63.5	254
マンニトール	15.5	62
ステアリン酸マグネシウム	1	4

【００８７】

（ｃ）ＦＣ錠の処方

単位：ｍｇ

成分	10mg錠	40mg錠
上記(ｂ)の裸錠	80	320
ヒドロキシプロピルメチルセルロース	1.3	2.6
酸化チタン	0.4	0.8
ポリエチレングリコール６０００	0.3	0.6
カルナバロウ	0.006	0.01

【００８８】

＜試験８＞

特許文献２の開示技術では１錠中にルラシドン・塩酸塩を４０ｍｇまで含有する製剤では同等の溶出挙動を示す経口製剤を提供できることを確認できた。ここでは、特許文献２の開示技術を用いて、部分アルファー化デンプンを含まない１錠中のルラシドン・塩酸塩含有量が８０ｍｇとなる製剤を試作した。錠剤の大型化は患者への負担を大きくするため、４０ｍｇ錠と同じ錠剤重量となるように、有効成分の含有率を２倍にすることにより製した。比較例１および２の結果は表４および図２に示した。

【００８９】
表４および図２から明らかなように、特許文献２の開示技術では、ｆ２の値から明らかなように、ルラシドン・塩酸塩の含有率を２倍にしたアルファ化デンプンを含まない８０ｍｇ錠では４０ｍｇ錠２錠と同等の溶出性を示すことはできなかった。
（ａ）顆粒の処方

単位：ｍｇ

成分	40mg錠	80mg錠
ルラシドン・塩酸塩	40	80
マンニトール	188	148
クロスカルメロースナトリウム	16	16
ヒドロキシプロピルメチルセルロース	10	10

【００９０】
（ｂ）裸錠の処方

単位：ｍｇ

成分	40mg錠	80mg錠
（ａ）の顆粒	254	254
マンニトール	62	62
ステアリン酸マグネシウム	4	4

【００９１】

（ｃ）ＦＣ錠の処方

単位：ｍｇ

成分	40mg錠	80mg錠
上記（ｂ）の裸錠	320	320
ヒドロキシプロピルメチルセルロース	2.6	2.6
酸化チタン	0.8	0.8
ポリエチレングリコール６０００	0.6	0.6
カルナバロウ	0.01	0.01

【００９２】
＜試験９＞
試験１の実施例１～３にて試作した含量の異なる３種類の製剤の溶出性を評価した。結果は、図３に示した。
図３から明らかなように、本発明により１錠中にルラシドン・塩酸塩を２０ｍｇから８０ｍｇを含有する製剤においても、錠剤の含量（力価）に依存しない同等の溶出性が確認された。
（ａ）造粒末の処方
【００９３】
【表２６】

単位：ｍｇ

成分	80mg錠	40mg錠	20mg錠
ルラシドン・塩酸塩	80	40	20
マンニトール	144	72	36
部分アルファ化デンプン	80	40	20
クロスカルメロースナトリウム	4	2	1
ヒドロキシプロピルメチルセルロース	8	4	2

【００９４】

（ｂ）打錠用顆粒/裸錠の処方

単位：ｍｇ

成分	80mg錠	40mg錠	20mg錠
上記（ａ）の顆粒	316	158	79
乳糖	−	−	−
ステアリン酸マグネシム	4	2	1

【００９５】

（ｃ）ＦＣ錠の処方

単位：ｍｇ

成分	80mg錠	40mg錠	20mg錠
上記(ｂ)の裸錠	320	160	80
ヒドロキシプロピルメチルセルロース	3.25	1.95	1.3
酸化チタン	1	0.6	0.4
ポリエチレングリコール６０００	0.75	0.45	0.3
カルナバロウ	0.01	0.006	0.004

【産業上の利用可能性】

【００９６】

本発明によりＮ－[４－〔４－(１，２－ベンズイソチアゾール－３－イル)－１－ピペラジニル〕－(２Ｒ，３Ｒ)－２，３－テトラメチレン－ブチル]－(１'Ｒ，２'Ｓ，３'Ｒ，４'Ｓ)－２，３－ビシクロ〔２，２，１〕ヘプタンジカルボキシイミド・塩酸塩（ルラシドン・塩酸塩）を有効成分とする崩壊性が良好な経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤を提供することが可能となった。

【図面の簡単な説明】

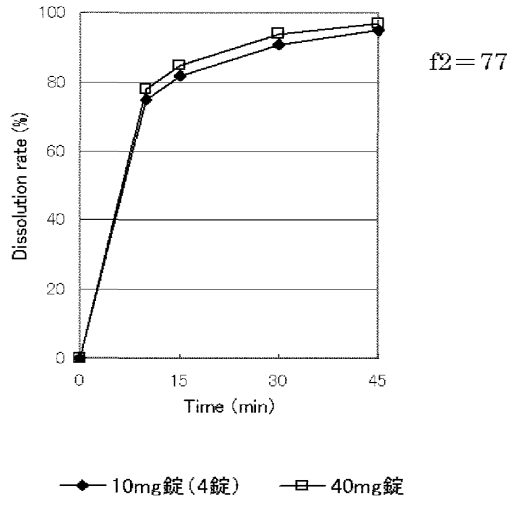
【００９７】

【図１】図1はルラシドン・塩酸塩を異なる含有量を有する製剤の溶出プロファイルの比較を示したものである。特許文献２の開示技術を用いて試作した１錠中のルラシドン・塩酸塩の含有量が１０ｍｇ（４錠）と４０ｍｇ（１錠）の製剤について溶出プロファイルを測定した。

【図２】図２は、ルラシドン・塩酸塩を異なる含有量を有する製剤の溶出プロファイルの比較を示したものである。特許文献２の開示技術を用いて試作した１錠中のルラシドン・塩酸塩の含有量が４０ｍｇ（２錠）と８０ｍｇ（１錠）の製剤について溶出プロファイルを測定した。

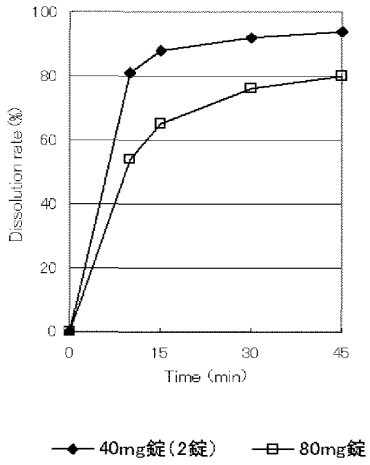
【図３】図３は、ルラシドン・塩酸塩を異なる含有量を有する製剤の溶出プロファイルの比較を示したものである。本発明の技術を用いて試作した１錠中のルラシドン・塩酸塩の含有量が２０ｍｇ（４錠）、４０ｍｇ（２錠）と８０ｍｇ（１錠）の製剤について溶出プロファイルを測定した。

【書類名】図面
【図１】



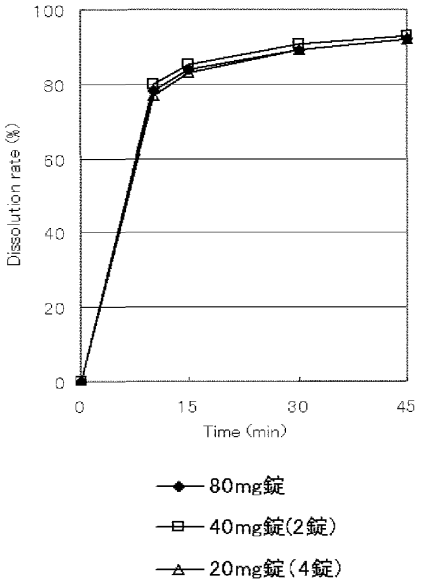
f2＝77

【図２】



f2＝37

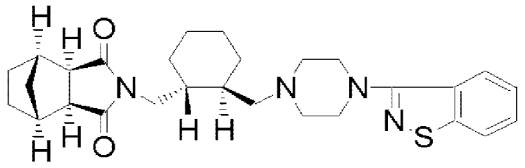
【図３】



f2＝88　(80 錠に対して 40mg 錠 2 錠)

f2＝97　(80 錠に対して 20mg 錠 4 錠)

【書類名】要約書
【要約】
【課題】　式（１）
【化１】



・HCl　(1)

で表されるＮ－[４－｛４－(１，２－ベンズイソチアゾール－３－イル)－１－ピペラジニル｝－(２Ｒ，３Ｒ)－２，３－テトラメチレン－ブチル]－(１'Ｒ，２'Ｓ，３'Ｒ，４'Ｓ)－２，３－ビシクロ｛２，２，１｝ヘプタンジカルボキシイミド・塩酸塩（ルラシドン・塩酸塩）を有効成分とする経口製剤において、有効成分の含量が変動しても、同等の溶出挙動を示す経口投与用製剤の提供。
【解決手段】　アルファ化デンプン類を含むことを特徴とする、ルラシドン・塩酸塩と水溶性賦形剤、水溶性高分子結合剤を含有する経口製剤は、経口投与された場合に、消化管内での有効成分の溶出性に優れ、かつ有効成分の含量が異なる製剤間で同等の溶出挙動を示すことができ、個々の患者に応じて最も適した薬剤の選択を可能にし、臨床上極めて有用である。
【選択図】なし

【書類名】　出願人名義変更届（一般承継）
【提出日】　平成17年10月26日
【あて先】　特許庁長官殿
【事件の表示】
　【出願番号】　特願2005-153508
【承継人】
　【識別番号】　000002912
　【氏名又は名称】　大日本住友製薬株式会社
　【代表者】　宮武　健次郎
　【電話番号】　06-6466-5214
【提出物件の目録】
　【物件名】　権利の承継を証明する書面　1
　【援用の表示】　なお、当該書面は、平成１７年１０月１９日付提出の平成１０年特許願第５４７９２７号の特許出願人名義変更届（一般承継）に添付した履歴事項全部証明書を援用し、省略する。

出願人履歴

０００１８３３７０
19900809
新規登録

大阪府大阪市中央区道修町２丁目２番８号
住友製薬株式会社
０００００２９１２
19900808
新規登録

大阪府大阪市中央区道修町２丁目６番８号
大日本製薬株式会社
０００００２９１２
20051003
名称変更

大阪府大阪市中央区道修町２丁目６番８号
大日本住友製薬株式会社

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/919,678	10/31/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	10/31/2007	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 23	Minus	** 24	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/YOLANDA CHADWICK/

Docket No.: 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

Application No.: 11/919,678 | Confirmation No.: 6965

Filed: October 31, 2007 | Art Unit: N/A

For: PHARMACEUTICAL COMPOSITION | Examiner: Not Yet Assigned

LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant wishes to advise the United States Patent and Trademark Office that the references cited in the International Search Report were previously filed on October 31, 2007.

As evidence of Applicant's previous submission of the references cited in the International Search Report in connection with the present application, Applicant encloses a copy of the postcard indicating receipt of the references cited in the International Search Report by the United States Patent and Trademark Office and payment of the appropriate fees by the Applicant.

However, we provide herewith a courtesy copy of the references filed on October 31, 2007.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Dated: March 14, 2008

Respectfully submitted,

By _____
Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant

Attachments: Copy of Postcard Receipt
SB-08
Copy of references submitted October 31, 2007

Atty Docket No.: 0020-5610PUS1

Inventor: Kazuyuki FUJIHARA

Application No.: NEW
Title: PHARMACEUTICAL COMPOSITION

Filing Date: October 31, 2007

21 / 919678

Documents Filed:

- PCT/IB/308 (2 sheets), PCT/IB/304, PCT/ISA/237 (4 sheets), PCT/ISA/210, Drawings (3 sheets)
- English language translation of the International application (48 pages)
- Oath or declaration of the inventor(s)
- Assignment (2 pages)
- Transmittal Letter to the United States Designated-Elected Office (3 pages)
- First Preliminary Amendment (6 pages)
- Information Disclosure Statement (2 pages)
- Recordation Form Cover Sheet (1 page)
- IDS (Citation) by Applicant (4 References) (1 page)
- Charge $1,590.00 to deposit account 02-2448

Via:
Sender's Initials: DRN//scp

Due Date: October 31, 2007
Date: October 31, 2007

Inventor: Kazuyuki FUJIHARA

Atty Docket No 0020-5610PUS1

Application No.: NEW
Title: PHARMACEUTICAL COMPOSITION

Filing Date: October 31, 2007

21

Documents Filed:

- PCT/IB/308 (2 sheets), PCT/IB/304, PCT/ISA/237 (4 sheets), PCT/ISA/210, Drawings (3 sheets)
- English language translation of the International application (48 pages)
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OIPE IAP97 OCT 31 2007 PATENT & TRADEMARK OFFICE

Via:
Sender's Initials: DRN//scp

Due Date: October 31, 2007
Date: October 31, 2007

Used in Lieu of PTO/SB/08A/B
(Based on PTO 01-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/919,678-Conf. #6965
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO 02/24166 A1	03-28-02			Abs
	BB	WO 2004/078173 A1	10-12-1990			Abs
	BC	JP-08-325146	12-10-1996			Abs

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Handbook of Pharmaceutical Excipients, 2nd edition, Vol. 491, The Pharmaceutical Press, 1994	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Birch, Stewart, Kolasch & Birch, LLP

DRN/kpc

Atty Docket No.: 0020-5610PUS1

Inventor: Kazuyuki FUJIHARA

Application No.: NEW
Title: PHARMACEUTICAL COMPOSITION

Filing Date: October 31, 2007

11/919678

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IAP07Rec'd PCT 31 OCT 2007

Via:
Sender's Initials: DRN//scp

Due Date: October 31, 2007
Date: October 31, 2007

Inventor: Kazuyuki FUJIHARA

Atty Docket No.: 0020-5610PUS1

21

Application No.: NEW
Title: PHARMACEUTICAL COMPOSITION

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- Recordation Form Cover Sheet (1 page)
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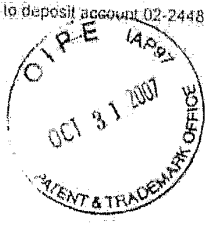

Via:
Sender's Initials: DRN//scp

Due Date: October 31, 2007
Date: October 31, 2007

Docket No.: 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

Application No.: 11/919,678 Confirmation No.: 6965

Filed: October 31, 2007 Art Unit: N/A

For: PHARMACEUTICAL COMPOSITION Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT
(SUBMISSION AFTER FILING OF AN APPLICATION BUT BEFORE FINAL REJECTION OR NOTICE OF ALLOWANCE OR CONCURRENTLY WITH A RULE 1.114 RCE APPLICATION)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. §§ 1.97 and 1.98, applicant(s) hereby submit(s) an Information Disclosure Statement for consideration by the Examiner.

I. LIST OF PATENTS, PUBLICATIONS OR OTHER INFORMATION

The patents, publications, or other information submitted for consideration by the Office are listed on the PTO-SB08(s), attached hereto.

II. COPIES

☐ a. Copies of cited U.S. patents and patent application publications are not included. Copies of foreign patent documents and non-patent literature are included.

☒ b. Some or all of the documents listed on the PTO-SB08 are not enclosed because they were cited in the International Search Report and copies should already be in the PTO file. If copies are needed, please contact the undersigned.

☐ c. REFERENCES PREVIOUSLY CITED OR SUBMITTED - Pursuant to 37 C.F.R. §1.98(d), consideration of information listed on the PTO-SB08 form(s) is requested since any patents, publications, or other information which are listed on the PTO-SB08 form(s) but for which copies are not enclosed herewith, were previously cited by or submitted to the PTO in one of the following applications which has been relied upon for an earlier filing date under 35 U.S.C. § 120:

III. CONCISE EXPLANATION OF THE RELEVANCE

(check at least one box)

☒ a. DOCUMENTS IN THE ENGLISH LANGUAGE – Some or all of the patents, publications, or other information listed on the attached PTO SB08 are in the English language and therefore, do not require a statement of relevancy.

☒ b. DOCUMENTS NOT IN THE ENGLISH LANGUAGE - A concise explanation of the relevance of all patents, publications, or other information listed that is not in the English language is as follows: **An English language abstract is provided for JP 2000-26292 A; US 5,532,372 corresponds to JP 28900953.**

☐ c. ENGLISH LANGUAGE SEARCH REPORT - An English language version of the search report or action that indicates the degree of relevance found by the foreign office is attached, thereby satisfying the requirement for a concise explanation. See MPEP 609(III)(A)(3).

☒ d. OTHER - The following additional information is provided for the Examiner's consideration. **Cite Nos. AA, CA and CB are cited in the Specification at page 3.**

IV. FEES (check one box)

☐ a. This Information Disclosure Statement is being filed concurrently with the filing of a new patent application; therefore, no fee is required.

☐ b. This Information Disclosure Statement is being filed concurrent with the filing of a continuation-in-part, continuation, or divisional patent application; therefore, no fee is required.

☐ c. This Information Disclosure Statement is being filed within three months of the filing date of a national application (37 C.F.R. § 1.97(b)(1)). No fee or statement is required. *(This section is not to be used with RCE's.)*

☐ d. This Information Disclosure Statement is being filed within three months of the date of entry of the national stage as set forth in § 1.491 in an international application (37 C.F.R. § 1.97(b)(2)). No fee or statement is required.

☐ e. This Information Disclosure Statement is being filed concurrently with the filing of a Request for Continued Examination under § 1.114 (37 C.F.R. § 1.97(b)(4)). No fee or statement is required.

☒ f. This Information Disclosure Statement is being filed before the mailing date of a first Action on the merits (37 C.F.R. § 1.97(b)(3)). **No fee or statement is required**. In the event that a first Office Action on the merits has been issued, please consider this IDS under 37 C.F.R. § 1.97(c) and see the statement under 37 C.F.R. § 1.97(e) below, or, if no statement has been made, charge our deposit account for the fee as required by 37 C.F.R. § 1.17(p).

☐ g. This Information Disclosure Statement is being filed before the mailing date of a Final Office Action under 37 C.F.R. § 1.113 (See 37 C.F.R. § 1.97(c)(1)) or before the mailing date of a Notice of Allowance under 37 C.F.R. § 1.311 (See 37 C.F.R. § 1.97(c)(2)).

☐ No statement; therefore, a fee as required by 37 C.F.R. § 1.17(p) is attached.

or

☐ See the statement below. No fee is required.

V. STATEMENT UNDER 37 C.F.R. § 1.97(e)

(check only one box)

The undersigned hereby states that:

☐ **a. Each item of information contained in the IDS was first cited in any communication from a foreign Patent Office in a counterpart foreign application not more than 30 days prior to the filing of this IDS; or**

☐ b. Each item of information contained in the IDS was first cited in any communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ c. No item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of IDS was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of the IDS.

☐ d. Some of the items of information were cited in a communication from a foreign Patent Office. As to this information, the undersigned states that each item of information contained in the IDS was first cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS. As to the remaining information, the undersigned hereby states that no item of this remaining information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application and, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

VI. PAYMENT OF FEES (check one box)

☐ The required fee is listed on the attached Fee Transmittal.

☒ No fee is required.

If the Examiner has any questions concerning this IDS, he/she is requested to contact the undersigned. If it is determined that this IDS has been filed under the wrong rule, the PTO is

requested to consider this IDS under the proper rule and charge the appropriate fee to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: MAR 14 2008

Respectfully submitted,

By _____

Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant

Attachment(s):
- ☒ PTO/SB/08
- ☒ Document(s)
- ☐ Foreign Search Report(s)
- ☐ Fee
- ☐ Other:

Used in Lieu of PTO/SB/08A/B
(Based on PTO 01-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/919,678-Conf. #6965
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-5,532,372-A	07-02-1996	Saji et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	JP-2000-26292-A	01-25-2000			Abs
	BB	JP-08-325146 A	10-12-1990			Abs

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Handbook of Pharmaceutical Excipients, 2nd edition, Vol. 491, The Pharmaceutical Press, 1994	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Birch, Stewart, Kolasch & Birch, LLP

DRN/kpc

Docket No.: 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

Application No.: 11/919,678 | Confirmation No.: 6965

Filed: October 31, 2007 | Art Unit: Not yet Assigned

For: PHARMACEUTICAL COMPOSITION | Examiner: Not yet Assigned

LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Subsequent to the filing of the above-identified application on October 31, 2007, attached hereto is an English translation of the International Preliminary Report on Patentability and Written Opinion of the International Searching Authority (Forms PCT/IB/326, PCT/IB/338, PCT/IB/373, PCT/ISA/237) that should be made of record in the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or to credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: MAR 14 2008

Respectfully submitted,

By _____
Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive, Suite 260
San Diego, California 92130
858 792-8855
Attorney for Applicants

Electronic Acknowledgement Receipt

EFS ID:	3007308
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutica compostion
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	2292
Filer:	Mark Jay Nuell/Kathleen Cassin
Filer Authorized By:	Mark Jay Nuell
Attorney Docket Number:	0020-5610PUS1
Receipt Date:	17-MAR-2008
Filing Date:	
Time Stamp:	12:14:25
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	2008031LETTER.pdf	284896 939b24bc4c80401178e93aa38f2961531c9ced22	no	4

Warnings:	
Information:	

This is not an USPTO supplied IDS fillable form					
2	Miscellaneous Incoming Letter	20080314Postcard.pdf	78870 9125093a0ae2001d885fcc6b2ebfcd5a90693b9a	no	1
Warnings:					
Information:					
3	Foreign Reference	20080314JP8325146.pdf	951605 a794ec5a03ab23573f12eaadc27dd2fd30cb1598	no	9
Warnings:					
Information:					
4	Foreign Reference	WO0224166.pdf	4354431 d9e71fcc7b1a3c3288f80f55c4d479a5d019d04f	no	49
Warnings:					
Information:					
5	Foreign Reference	WO2004078173.pdf	1913456 10ba907d7eea888dfaab6f8bd650adbdd55413bd	no	23
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Filed	20080314IDS.pdf	514743 aec00aff93600b064ced9b88219e23e05904b73e	no	6
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This is not an USPTO supplied IDS fillable form					
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Warnings:					
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8	NPL Documents	20080314PregelatinizedStarch.pdf	531503 f8b1100d5669682ba230cbcf7d9e8f220c07572c	no	3
Warnings:					
Information:					
9	Information Disclosure Statement Letter	20080314LetterWO.pdf	95195 fdac3df7ca9f345809482ca5118c938b57b64ed5	no	2
Warnings:					
Information:					

10	Miscellaneous Incoming Letter	20080314TransofWO.pdf	475204 4453725581214d69a1a010c614efad7b71a1514a	no	5
Warnings:					
Information:					
			Total Files Size (in bytes):	10357754	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 11/919,678

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	LARGE ENTITY RATE	LARGE ENTITY FEE
U.S. NATIONAL STAGE FEES							
BASIC FEE			BASIC FEE		OR	BASIC FEE	310
EXAMINATION FEE			EXAM. FEE			EXAM. FEE	210
SEARCH FEE			SEARCH FEE			SEARCH FEE	410
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =	X $ 125 =			X $ 250 =	
TOTAL CHARGEABLE CLAIMS	24 minus 20 =	4	X $ 25 =		OR	X $ 50 =	200
INDEPENDENT CLAIMS	5 minus 3 =	2	X $ 100 =		OR	X $ 200 =	420
MULTIPLE DEPENDENT CLAIM PRESENT		☐	+ $ 180 =		OR	+ $ 360 =	
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL		OR	TOTAL	1,550

CLAIMS AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
AMENDMENT A	Total	*	Minus	**	=	X $ 25 =		OR	X $ 50 =	
	Independent	*	Minus	***	=	X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐	+ $ 180 =		OR	+ $ 360 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
AMENDMENT B	Total	*	Minus	**	=	X $ 25 =		OR	X $ 50 =	
	Independent	*	Minus	***	=	X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐	+ $ 180 =		OR	+ $ 360 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO. 11/919678

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		1			
2	1		1			
3	1		1			
4		3		1		
5	1		1			
6	1		1			
7		6		1		
8				1		
9				1		
10				1		
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TOTAL IND.	5		5			
TOTAL DEP.	21		19			
TOTAL CLAIMS	26		24			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
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TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

U.S NATIONAL STAGE WORKSHEET (DO/EO)

U.S. APPL. NO. 11/919678 INTERNATIONAL APPL. JP06/310571

APPLICATION FILED BY: 20 MOS., ____ OR 30 MOS., X SCREENED BY

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- X International application
- ___ Article 19 amendments
- X Priority Document(s) No. 1
- ___ Request Form PCT/RO/101
- ___ PCT/IB/302
- X PCT/IB/304
- ___ PCT/IB/306
- X PCT/IB/308
- ___ PCT/IB/331
- ___ OTHER PCT/IB/ 237
- ___ PCT/IPEA/409 also 416
- ___ 409 annexes to IPER
- X PCT/ISA/210 (Search report)
- ___ Search report References
- ___ Other Papers filed

WIPO PUBLICATION
PUBLICATION NO. WO 06/126681
PUBLICATION DATE 30 NOV 06
PUBLICATION LANG., JAPANESE
NOT PUBLISHED
___ U.S. only ___ Requested

RECEIVED FROM THE APPLICANT: (other than checked above)

- X National application basic fee paid
- X Express Processing Requested
- X Translation of the International Application
- ___ Used the IB copy of the IA
- X Description
- X Claims
- X Drawings 3
- ___ Foreign Language in drawing
- ___ Article 19 Amendments
- ___ Amendment used in application
- ___ Article 34 Amendment
- ___ Amendment used in application
- ___ DNA
- ___ 1194 transaction done
- X Preliminary Amendment(s) filed 31 OCT 2007
  - ___ second submission ___
- X Information Disclosure Statement(s) 31 OCT 2007
  - X second submission 3-17-08
- X Assignment
  - ___ Forward to Assignment Branch
- ___ Substitute Specification ___
- ___ Small Entity Statement ___
  - type ___
- X Oath/Declaration (date submitted) 31 OCT 2007
  - ___ Not executed
  - X Executed
- ___ Power of Attorney
- ___ Change of Address

35 USC Receipt of Request (PTO – 1399 Transmittal Letter)	31 OCT 2007
Date Acceptable oath/declaration received	31 OCT 2007
102(e) Date	31 OCT 2007
Date complete 35 USC 371 requirements met	31 OCT 2007

DATE NOTICE COMPLETED

DO/EO 903	Notice of Acceptance
DO/EO 905	Notice of Missing Requirements
DO/EO 917	Notice of A defective oath or declaration
DO/EO 916	Notice of defective response
DO/EO 913	Notice of defective translation
DO/EO 909	Notification of Abandonment

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
11/919,678	Kazuyuki Fujihara	0020-5610PUS1

2292
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

INTERNATIONAL APPLICATION NO.	
PCT/JP2006/310571	
I.A. FILING DATE	PRIORITY DATE
05/26/2006	05/26/2005

CONFIRMATION NO. 6965
371 ACCEPTANCE LETTER

OC000000034683897

Date Mailed: 02/25/2009

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

10/31/2007	10/31/2007
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 10/31/2007
- English Translation of the IA filed on 10/31/2007
- Copy of the International Search Report filed on 10/31/2007
- Preliminary Amendments filed on 10/31/2007
- Information Disclosure Statements filed on 10/31/2007
- Oath or Declaration filed on 10/31/2007
- Request for Immediate Examination filed on 10/31/2007
- U.S. Basic National Fees filed on 10/31/2007
- Assignment filed on 10/31/2007
- Priority Documents filed on 10/31/2007
- Specification filed on 10/31/2007
- Claims filed on 10/31/2007
- Abstracts filed on 10/31/2007
- Drawings filed on 10/31/2007

FORM PCT/DO/EO/903 (371 Acceptance Notice)

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

VONDA M WALLACE

Telephone: (703) 308-9140 EXT 225

FORM PCT/DO/EO/903 (371 Acceptance Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/919,678	10/31/2007		1550	0020-5610PUS1	24	5

CONFIRMATION NO. 6965

2292
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

FILING RECEIPT

OC000000034683896

Date Mailed: 02/25/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Kazuyuki Fujihara, Osaka-fu, JAPAN;

Power of Attorney: The patent practitioners associated with Customer Number 02292

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/JP2006/310571 05/26/2006

Foreign Applications

JAPAN 2005-153508 05/26/2005

If Required, Foreign Filing License Granted: 02/23/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/919,678**

Projected Publication Date: 06/04/2009

Non-Publication Request: No

Early Publication Request: No

Title

Pharmaceutical composition

Preliminary Class

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier

license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/919,678	10/31/2007	Kazuyuki Fujihara	0020-5610PUS1

CONFIRMATION NO. 6965

2292
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

PUBLICATION NOTICE

OC000000036304343

Title: Pharmaceutical composition

Publication No.US-2009-0143404-A1
Publication Date:06/04/2009

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	0020-5610PUS1	6965

2292 7590 08/07/2009
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
08/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	11/919,678	FUJIHARA, KAZUYUKI	
	Examiner	Art Unit	
	SARAH PIHONAK	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-24 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-4, and 8-24, drawn to an oral preparation comprised of lurasidone.

Group II, claim(s) 5-7, drawn to a method of granulation of a powder mixture comprised of lurasidone.

2. As set forth in Rule 13.1 of the Patent Cooperation Treaty (PCT), "the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept." Moreover, as stated in PCT Rule 13.2, "where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features." Furthermore, Rule 13.2 defines "special technical features" as "those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

3. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is an oral preparation comprised of lurasidone, a pregelatinized starch component, and a water-soluble polymer. The oral preparation of claim 1 does not present a contribution over the prior art, as it is disclosed in WO 01/076557 (p. 1, claims 1-3 and 11, English translation; particularly, third line of claim 11, regarding compound SM-13496). Claims 1-3 and 11 of the WO 01/076557 patent application are drawn to an oral composition comprised of SM-13496, which is the hydrochloride salt of lurasidone, as well as a starch component and a water soluble polymer. Therefore, instant claim 1 is not novel over the prior art. As such, Group I does not share a special technical feature with the instant claims of Group II. Therefore, the claims are not so linked within the meaning of PCT Rule 13.2 so as to form a single inventive concept, and unity between Groups I-II is broken.

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process

claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST, with Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

Notice of References Cited	Application/Control No. 11/919,678	Applicant(s)/Patent Under Reexamination FUJIHARA, KAZUYUKI	
	Examiner SARAH PIHONAK	Art Unit 1617	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 01/76557A1	10-2001	World Intellect	Kobayashi et. al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Docket No. 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

Application No. 11/919,678 Confirmation No. 6965

Filed: October 31, 2007 Art Unit: 1617

For: PHARMACEUTICAL COMPOSITION Examiner: S. Pihonak

RESPONSE TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following Remarks are submitted in reply to the Restriction Requirement mailed August 7, 2009.

Remarks begin on page 2 of this paper.

REMARKS

The Examiner has required restriction of the present claims to one of

Group I, claims 1-4 and 8-24, directed to an oral preparation comprising lurasidone; and

Group II, claims 5-7, directed to a method of making a granulated composition comprising lurasidone.

Applicants hereby elect, without traverse, the claims of Group I, claims 1-4 and 8-24, for prosecution in the present invention.

Applicants submit that, should the claims of Group I be found allowable, the claims of Group II, if commensurate in scope with the allowable claims, should be rejoined to the present application for examination. MPEP 821.04.

The Examiner has asserted that the present invention lacks novelty over WO 01/076557. The Examiner points to claims 1-3 and 11 of the reference.

Applicants note that the present invention is claimed as described as a composition comprising at least "a pregelatinized starch", and that such an ingredient does not appear to be disclosed in WO 01/076557. Accordingly, the present invention is novel of WO 01/076557 for at least this reason.

Favorable action on the merits of the present application is requested.

If allowance of the claims is precluded by some minor issue that can be resolved by telephone discussion, the Examiner is invited to contact the undersigned at the telephone number below to discuss the matter.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or to credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: August 24, 2009

Respectfully submitted,

By /mjn/
Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive, Suite 260
San Diego, California 92130
858 792-8855
Attorney for Applicants

Electronic Acknowledgement Receipt

EFS ID:	5942202
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	02292
Filer:	Mark Jay Nuell
Filer Authorized By:	
Attorney Docket Number:	0020-5610PUS1
Receipt Date:	24-AUG-2009
Filing Date:	31-OCT-2007
Time Stamp:	20:57:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		20090824IDSwSB08.pdf	511363 f34c29a553400583 26d770aab05efebad1515e0e	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	5
	Information Disclosure Statement (IDS) Filed (SB/08)	6	6

Warnings:					
Information:					
2	NPL Documents	Chueshov1999.pdf	459306 5411af6a44268aad8d3624fcddb89e19e63e202b	no	4
Warnings:					
Information:					
3	NPL Documents	RussianOA.pdf	496333 c597cafc72fe74d33fd1fa280d4ae34d334b0a97	no	7
Warnings:					
Information:					
4	Response to Election / Restriction Filed	20090824RespRestrictReq.pdf	161920 103c5ab59339c14dc1a9f706b72a5e00521d6677	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	1628922		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

Application No. 11/919,678 | Confirmation No. 6965

Filed: October 31, 2007 | Art Unit: 1617

For: PHARMACEUTICAL COMPOSITION | Examiner: S. Pihonak

INFORMATION DISCLOSURE STATEMENT
(SUBMISSION AFTER FILING OF AN APPLICATION BUT BEFORE FINAL REJECTION OR NOTICE OF ALLOWANCE OR CONCURRENTLY WITH A RULE 1.114 RCE APPLICATION)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

Pursuant to 37 C.F.R. §§ 1.97 and 1.98, applicant(s) hereby submit(s) an Information Disclosure Statement for consideration by the Examiner.

I. LIST OF PATENTS, PUBLICATIONS OR OTHER INFORMATION

The patents, publications, or other information submitted for consideration by the Office are listed on the PTO-SB08(s), attached hereto.

II. COPIES

☒ a. Copies of cited U.S. patents and patent application publications are not included. Copies of foreign patent documents and non-patent literature are included.

☐ b. Some or all of the documents listed on the PTO-SB08 are not enclosed because they were cited in the International Search Report and copies should already be in the PTO file. If copies are needed, please contact the undersigned.

☐ c. REFERENCES PREVIOUSLY CITED OR SUBMITTED - Pursuant to 37 C.F.R. §1.98(d), consideration of information listed on the PTO-SB08 form(s) is requested since any patents, publications, or other information which are listed on the PTO-SB08 form(s) but for which copies are not enclosed herewith, were previously cited by or submitted to the PTO in one of the following applications which has been relied upon for an earlier filing date under 35 U.S.C. § 120:

III. CONCISE EXPLANATION OF THE RELEVANCE

(check at least one box)

☐ a. DOCUMENTS IN THE ENGLISH LANGUAGE – Some or all of the patents, publications, or other information listed on the attached PTO SB08 are in the English language and therefore, do not require a statement of relevancy.

☒ b. DOCUMENTS NOT IN THE ENGLISH LANGUAGE - A concise explanation of the relevance of all patents, publications, or other information listed that is not in the English language is as follows: **English translation of Page 10, lines 1-14 and lines 37-43; and of page 11, lines 25-28 of Russian non-Patent Literature reference is provided.**

☐ c. ENGLISH LANGUAGE SEARCH REPORT - An English language version of the search report or action that indicates the degree of relevance found by the foreign office is attached, thereby satisfying the requirement for a concise explanation. See MPEP 609(III)(A)(3).

☒ d. OTHER - The following additional information is provided for the Examiner's consideration: **Russian Official Action with English translation.**

IV. FEES (check one box)

☐ a. This Information Disclosure Statement is being filed concurrently with the filing of a new patent application; therefore, no fee is required.

☐ b. This Information Disclosure Statement is being filed concurrent with the filing of a continuation-in-part, continuation, or divisional patent application; therefore, no fee is required.

☐ c. This Information Disclosure Statement is being filed within three months of the filing date of a national application (37 C.F.R. § 1.97(b)(1)). No fee or statement is required. *(This section is not to be used with RCE's.)*

☐ d. This Information Disclosure Statement is being filed within three months of the date of entry of the national stage as set forth in § 1.491 in an international application (37 C.F.R. § 1.97(b)(2)). No fee or statement is required.

☐ e. This Information Disclosure Statement is being filed concurrently with the filing of a Request for Continued Examination under § 1.114 (37 C.F.R. § 1.97(b)(4)). No fee or statement is required.

☒ f. This Information Disclosure Statement is being filed before the mailing date of a first Action on the merits (37 C.F.R. § 1.97(b)(3)). No fee or statement is required. In the event that a first Office Action on the merits has been issued, please consider this IDS under 37 C.F.R. § 1.97(c) and see the statement under 37 C.F.R. § 1.97(e) below, or, if no statement has been made, charge our deposit account for the fee as required by 37 C.F.R. § 1.17(p).

☐ g. This Information Disclosure Statement is being filed before the mailing date of a Final Office Action under 37 C.F.R. § 1.113 (See 37 C.F.R. § 1.97(c)(1)) or before the mailing date of a Notice of Allowance under 37 C.F.R. § 1.311 (See 37 C.F.R. § 1.97(c)(2)).

☐ No statement; therefore, a fee as required by 37 C.F.R. § 1.17(p) is attached.

or

☐ See the statement below. No fee is required.

V. STATEMENT UNDER 37 C.F.R. § 1.97(e)

(check only one box)

The undersigned hereby states that:

☐ **a. Each item of information contained in the IDS was first cited in any communication from a foreign Patent Office in a counterpart foreign application not more than 30 days prior to the filing of this IDS; or**

☐ b. Each item of information contained in the IDS was first cited in any communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ c. No item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of IDS was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of the IDS.

☐ d. Some of the items of information were cited in a communication from a foreign Patent Office. As to this information, the undersigned states that each item of information contained in the IDS was first cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS. As to the remaining information, the undersigned hereby states that no item of this remaining information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application and, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

VI. PAYMENT OF FEES (check one box)

☐ The required fee is listed on the attached Fee Transmittal.

☒ No fee is required.

If the Examiner has any questions concerning this IDS, he/she is requested to contact the undersigned. If it is determined that this IDS has been filed under the wrong rule, the PTO is

requested to consider this IDS under the proper rule and charge the appropriate fee to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: August 24, 2009

Respectfully submitted,

By _____

Mark J. Nuell
Registration No. 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive, Suite 260
San Diego, California 92130
(703) 205-8000
Attorney for Applicant

Attachments:

- ☒ PTO/SB/08
- ☒ Documents
- ☐ Fee Transmittal
- ☐ Other:

PTO/SB/08b (06-09)
Approved for use through 07/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/919,678-Conf. #6965
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	1617
Examiner Name	S. Pihonak
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Chueshov, V. I., et al., "Manufacturing Technologies of Drugs," Promyshlennaya Technologiya Lekarstv, Vol 2, pp 10-11 (1999).	part
	CB	Russian Official Action	part

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (06-09)
Approved for use through 07/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/919,678-Conf. #6965
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	1617
Examiner Name	S. PIHONAK
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA*	JP-2000-26292-A	01-25-2000			
	BB	EP-1327440-A1	07-16-2003	Sumitomo Pharma		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Makino, T., et al., "Importance of Gelatinization Degree of Starch Past Binder in Hardness and Disintegration Time of Tablets," Chem. Pharm. Bull., Vol 43, No 3, pp 514-116 (1995)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	6143364
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	02292
Filer:	Mark Jay Nuell/Leila Landa
Filer Authorized By:	Mark Jay Nuell
Attorney Docket Number:	0020-5610PUS1
Receipt Date:	24-SEP-2009
Filing Date:	31-OCT-2007
Time Stamp:	22:28:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		20090925IDSwSB08.pdf	513755 04c3a7dc48c13ccb2f59d9ca9e5ea23abedc2ae7	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	5
	Information Disclosure Statement (IDS) Filed (SB/08)	6	6

Warnings:					
Information:					
2	Foreign Reference	EP1327440A1.pdf	1406997 d764aac5fb347bc4fc2fd3fe155ef1b68ae2aab5	no	32
Warnings:					
Information:					
3	NPL Documents	Makino1995.pdf	497316 dd1ed15daeac6a24dfa6b2a03675839673e415cc	no	3
Warnings:					
Information:					
4	NPL Documents	EPOSearchReport.pdf	440972 6a7b4fd3430cde18337cbb5dc58ab1a74d92370d	no	6
Warnings:					
Information:					
		Total Files Size (in bytes):	2859040		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 0020-5610PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazuyuki FUJIHARA

Application No. 11/919,678 | Confirmation No. 6965

Filed: October 31, 2007 | Art Unit: 1617

For: PHARMACEUTICAL COMPOSITION | Examiner: S. Pihonak

INFORMATION DISCLOSURE STATEMENT
(SUBMISSION AFTER FILING OF AN APPLICATION BUT BEFORE FINAL REJECTION OR NOTICE OF ALLOWANCE OR CONCURRENTLY WITH A RULE 1.114 RCE APPLICATION)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

Pursuant to 37 C.F.R. §§ 1.97 and 1.98, applicant(s) hereby submit(s) an Information Disclosure Statement for consideration by the Examiner.

I. LIST OF PATENTS, PUBLICATIONS OR OTHER INFORMATION

The patents, publications, or other information submitted for consideration by the Office are listed on the PTO-SB08(s), attached hereto.

II. COPIES

☒ a. Copies of cited U.S. patents and patent application publications are not included. Copies of foreign patent documents and non-patent literature are included.

☐ b. Some or all of the documents listed on the PTO-SB08 are not enclosed because they were cited in the International Search Report and copies should already be in the PTO file. If copies are needed, please contact the undersigned.

☐ c. REFERENCES PREVIOUSLY CITED OR SUBMITTED - Pursuant to 37 C.F.R. §1.98(d), consideration of information listed on the PTO-SB08 form(s) is requested since any patents, publications, or other information which are listed on the PTO-SB08 form(s) but for which copies are not enclosed herewith, were previously cited by or submitted to the PTO in one of the following applications which has been relied upon for an earlier filing date under 35 U.S.C. § 120:

III. CONCISE EXPLANATION OF THE RELEVANCE

(check at least one box)

☒ a. DOCUMENTS IN THE ENGLISH LANGUAGE – Some or all of the patents, publications, or other information listed on the attached PTO SB08 are in the English language and therefore, do not require a statement of relevancy.

☐ b. DOCUMENTS NOT IN THE ENGLISH LANGUAGE - A concise explanation of the relevance of all patents, publications, or other information listed that is not in the English language is as follows:

☐ c. ENGLISH LANGUAGE SEARCH REPORT - An English language version of the search report or action that indicates the degree of relevance found by the foreign office is attached, thereby satisfying the requirement for a concise explanation. See MPEP 609(III)(A)(3).

☒ d. OTHER - The following additional information is provided for the Examiner's consideration: European Search Report.

IV. FEES (check one box)

☐ a. This Information Disclosure Statement is being filed concurrently with the filing of a new patent application; therefore, no fee is required.

☐ b. This Information Disclosure Statement is being filed concurrent with the filing of a continuation-in-part, continuation, or divisional patent application; therefore, no fee is required.

☐ c. This Information Disclosure Statement is being filed within three months of the filing date of a national application (37 C.F.R. § 1.97(b)(1)). No fee or statement is required. *(This section is not to be used with RCE's.)*

☐ d. This Information Disclosure Statement is being filed within three months of the date of entry of the national stage as set forth in § 1.491 in an international application (37 C.F.R. § 1.97(b)(2)). No fee or statement is required.

☐ e. This Information Disclosure Statement is being filed concurrently with the filing of a Request for Continued Examination under § 1.114 (37 C.F.R. § 1.97(b)(4)). No fee or statement is required.

☒ f. This Information Disclosure Statement is being filed before the mailing date of a first Action on the merits (37 C.F.R. § 1.97(b)(3)). No fee or statement is required. In the event that a first Office Action on the merits has been issued, please consider this IDS under 37 C.F.R. § 1.97(c) and see the statement under 37 C.F.R. § 1.97(e) below, or, if no statement has been made, charge our deposit account for the fee as required by 37 C.F.R. § 1.17(p).

☐ g. This Information Disclosure Statement is being filed before the mailing date of a Final Office Action under 37 C.F.R. § 1.113 (See 37 C.F.R. § 1.97(c)(1)) or before the mailing date of a Notice of Allowance under 37 C.F.R. § 1.311 (See 37 C.F.R. § 1.97(c)(2)).

☐ No statement; therefore, a fee as required by 37 C.F.R. § 1.17(p) is attached.

or

☐ See the statement below. No fee is required.

V. STATEMENT UNDER 37 C.F.R. § 1.97(e)

(check only one box)

The undersigned hereby states that:

☐ **a. Each item of information contained in the IDS was first cited in any communication from a foreign Patent Office in a counterpart foreign application not more than 30 days prior to the filing of this IDS; or**

☐ b. Each item of information contained in the IDS was first cited in any communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ c. No item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of IDS was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of the IDS.

☐ d. Some of the items of information were cited in a communication from a foreign Patent Office. As to this information, the undersigned states that each item of information contained in the IDS was first cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS. As to the remaining information, the undersigned hereby states that no item of this remaining information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application and, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

VI. PAYMENT OF FEES (check one box)

☐ The required fee is listed on the attached Fee Transmittal.

☒ No fee is required.

If the Examiner has any questions concerning this IDS, he/she is requested to contact the undersigned. If it is determined that this IDS has been filed under the wrong rule, the PTO is

requested to consider this IDS under the proper rule and charge the appropriate fee to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: SEP 2 5 2009

Respectfully submitted,

By _____

Mark J. Nuell
Registration No. 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive, Suite 260
San Diego, California 92130
(703) 205-8000
Attorney for Applicant

Attachment:
- ☒ PTO/SB/08
- ☒ Document
- ☒ Foreign Search Report
- ☐ Fee
- ☐ Other:

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	0020-5610PUS1	6965

2292 7590 11/30/2009

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	11/919,678	FUJIHARA, KAZUYUKI	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *5-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/2007 3/17/2008 3/17/2008 8/24/2008 9/24/2009*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application, filed 10/31/2007, is a national stage entry of PCT/JP2006/310571, filed on 5/26/2006.

Priority

This application claims foreign priority to Application No. 2005-153508, filed on 5/26/2005.

Response to Restriction Requirement

1. Applicant's election without traverse of the invention of Group I, claims 1-4 and 8-24, in the reply filed on 9/24/2009 is acknowledged.

2. Claims 5-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/24/2009.

3. Applicant is reminded that, in the event that the claims of Group I are found allowable, a rejoinder of the withdrawn method claims of Group II will be considered.

4. Claims 1-4 and 8-24 were examined.

5. Claims 1-4 and 8-24 are rejected.

Claim Rejections-35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-4 and 8-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujihara et. al., EP Patent Publication No. 1327440, in view of Salpekar et. al., US Patent No. 4,600,579. The reference of Fujihara et. al. was submitted by the Applicants in the Information Disclosure Statement.

The claims are drawn to an oral composition comprised of lurasidone, pregelatinized starch, a water soluble excipient such as mannitol or lactose, and a water soluble polymer binder. The claims are also drawn to the composition in which the pregelatinized starch is present in an amount from 10-50% by weight, and in which the lurasidone is present in an amount from 25 to 45% by weight.

Fujihara et. al. teaches an oral composition comprised of a slightly water soluble active ingredient, such as lurasidone, along with a first disintegrant, a second disintegrant, and a water soluble polymer binder (Abstract; p. 4-5, paragraph [0008]). Fujihara et. al. teaches that the composition provides advantageous dissolution characteristics when ingested (Abstract). It is taught that one of the water soluble excipients includes sugar alcohols such as mannitol or lactose (p. 3, paragraph [0017],

item (18); p. 5, paragraph [0014]). The other disintegrant is taught as including excipients such as microcrystalline cellulose, croscarmellose sodium, among others (p. 5, paragraph [0011]), and the water soluble polymer binder includes polyvinylpyrrolidone, polyvinyl alcohol, and others (p. 5, paragraph [0010]). It is taught that the amount of lurasidone present in the oral composition is 40 mg., which is within the range instantly claimed (p. 5, paragraph [0015]; p. 22, paragraph [0152], Table 28), and that the average particle size of lurasidone is between 0.5 to 5 μm, which meets the limitations of claim 22 (p. 6, paragraph [0021]). It is taught that for a tablet of a weight of approximately 142 mg., the amount of lurasidone present is 40 mg., which is approximately 28 % of the weight of the composition (p. 29, paragraph [0194], Table 44), which meets the limitations of claims 10 and 11. The amount of the disintegrants present in the composition is taught as ranging from 5 to 300 % by weight of the composition (p. 4, paragraph [0007], item (33)), or up to 1200% by weight (p. 6, paragraph [0029]). It is taught that the oral preparation comprises a granule, which is prepared by granulating the water-soluble polymer binder with the powdery mixture consisting of the active agent (lurasidone), a water soluble excipient, and another disintegrant (p. 3, paragraph [0007], items (11-13); p. 4, paragraph [0007], item (40)). Fujihara et. al. teaches that the preparation can be formulated as pills, granules, fine granules, capsules, tablets, etc. (p. 5, paragraph [0016]).

Fujihara et. al. does not explicitly teach that the composition comprises pregelatinized starch, in an amount from 10 to 50% by weight of the composition.

Salpekar et. al. teaches a composition comprised of a pharmaceutically active ingredient, a lubricant, a disintegrant, and pregelatinized starch allows for high hardness, and short dissolution time when ingested (Abstract). Salpekar et. al. teaches that the composition comprised of the pregelatinized starch is beneficial for preparing oral pharmaceutical formulations such as tablets (column 1, lines 22-29). It is taught that the partially pregelatinized starch, such as the starch commercially known as Starch 1500, acts as a binder to the composition, and provides beneficial disintegrant properties, as well as increasing hardness of the composition and shortening the dissolution and disintegration time (column 3, lines 38-51; column 4, lines 31-37). Salpekar et. al. teaches that the amount of partially pregelatinized starch ranges from 5 or less to 15 or more parts per 100 parts of the composition (column 4, lines 15-17), which is within the amount of pregelatinized starch instantly claimed. It is taught that the amount of pregelatinized starch present is based upon the amount necessary to impart the high hardness and decreased dissolution times to the composition (column 4, lines 3-9); therefore, it would have been obvious to one of ordinary skill in the art that the optimum range of the pregelatinized starch may comprise amounts greater than or less than 5-15 % by weight, as taught. Salpekar et. al. teaches that the percent gelatinization of the pregelatinized starch ranges optimally from 50 to 75% (column 2, lines 33-55), which is within the percent range cited in claim 21. Additionally, it is taught that Starch 1500 has a moisture content between 3 and 5 % (column 3, lines 38-45), which meets the limitations of claim 22.

One of ordinary skill in the art would have been motivated, at the time of the invention, to prepare the oral lurasidone preparation taught by Fujihara et. al. with the pregelatinized starch excipient taught by Salpekar et. al. because Salpekar et. al. teaches that the pregelatinized starch in oral pharmaceutical formulations provides beneficial properties, such as increased hardness of the tablet, decreased dissolution time after ingestion, and short disintegration time. As such, it would have been prima facie obvious for one of ordinary skill in the art to prepare the oral lurasidone composition as taught by Fujihara et. al. with the pregelatinized starch excipient as taught by Salpekar et. al. because both Fujihara et. al. and Salpekar et. al. teach pharmaceutical compositions formulated for oral administration. Therefore, there would have been an expectation of success in utilizing the pregelatinized excipient for the composition comprising lurasidone, because it is taught by Salpekar et. al. that the pregelatinized starch imparts beneficial properties to oral formulations.

Information Disclosure Statements

9. The information disclosure statements (IDS) submitted on 10/31/2007, 3/17/2008, 8/24/2009, and 9/24/2009 were filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST, with Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 11/919,678	Applicant(s)/Patent Under Reexamination FUJIHARA, KAZUYUKI	
	Examiner SARAH PIHONAK	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,600,579	07-1986	Salpekar et al.	514/629
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/13/2009								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	N								
	6	N								
	7	N								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								
	15	✓								
	16	✓								
	17	✓								
	18	✓								
	19	✓								
	20	✓								
	21	✓								
	22	✓								
	23	✓								
	24	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search in EAST, PALM	11/12/2009	S.P.
Invention and claims search in EAST, STN	11/12/2009	S.P.

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/S. P./ Examiner.Art Unit 1627	

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CONFIRMATION NO. 6965

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/919,678	10/31/2007	514	1627	0020-5610PUS1

APPLICANTS
Kazuyuki Fujihara, Osaka-fu, JAPAN;

**** CONTINUING DATA ***************************
This application is a 371 of PCT/JP2006/310571 05/26/2006

**** FOREIGN APPLICATIONS ***************************
JAPAN 2005-153508 05/26/2005

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
02/23/2009

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /SARAH PIHONAK/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		JAPAN	5	24	5

ADDRESS
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747
UNITED STATES

TITLE
Pharmaceutical composition

FILING FEE RECEIVED		
1550	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	4	"2001076557".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2009/07/17 07:52
S2	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:53
S3	2622	pre-gelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S4	0	S2 and S3	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S5	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S6	25	S2 and S5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:55
S7	234938	oral and pharmaceutical	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S8	10067	S5 and S7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S9	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01

EAST Search History (Prior Art)

S10	446	S9 and oral	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:02
S11	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:17
S12	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S13	1	S11 and S12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S14	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S15	86	S11 and S14	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S16	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:57
S17	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S18	86	S16 and S17	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S19	1	"3607394".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2009/11/12 14:11

EAST Search History (Prior Art)

S20	67	(pregelatin$4 with starch) same (polymer with binder)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:29
S21	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S22	745	S21 and (starch adj "1500")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S23	47786	water adj solub$4 adj polymer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40
S24	43	S22 and S23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40
S25	99	S21 and (PCS)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:42
S26	5	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2009/11/12 15:05
S27	4	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2009/11/12 15:07
S28	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S29	1747	S28 and (water or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S30	202	S28 with (water or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:15

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 1

Complete if Known	
Application Number	11/919,678-Conf. #6965
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO 02/24166 A1	03-28-02			Abs
	BB	WO 2004/078173 A1	10-12-1990			Abs
	BC	JP-08-325146	12-10-1996			Abs

Examiner Signature		Date Considered	

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	CA	Handbook of Pharmaceutical Excipients, 2nd edition, Vol. 491, The Pharmaceutical Press, 1994	

Examiner Signature	/Sarah Pihonak/	Date Considered	11/13/2009

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Birch, Stewart, Kolasch & Birch, LLP DRN/kpc

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Sheet 1 of 1

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Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	0020-5610PUS1

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	AA*	US-5,532,372-A	07-02-1996	Saji et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	JP-2000-26292-A	01-25-2000			Abs
	BB	JP-08-325146 A	10-12-1990			Abs

Examiner Signature		Date Considered	

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	CA	Handbook of Pharmaceutical Excipients, 2nd edition, Vol. 491, The Pharmaceutical Press, 1994	

Examiner Signature	/Sarah Pihonak/	Date Considered	11/13/2009

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Approved for use through 07/31/2009. OMB 0651-0031
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Sheet 1 of 1

Complete if Known	
Application Number	11/919,678-Conf. #6965
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	1617
Examiner Name	S. Pihonak
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

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NON PATENT LITERATURE DOCUMENTS

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	CA	Chueshov, V. I., et al., "Manufacturing Technologies of Drugs," Promyshlennaya Technologiya Lekarstv, Vol 2, pp 10-11 (1999).	part
	CB	Russian Official Action	part

Examiner Signature	/Sarah Pihonak/	Date Considered	11/13/2009

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Birch, Stewart, Kolasch & Birch, LLP

DRN/ll

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PTO/SB/08b (06-09)
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Sheet 1 of 1

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Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	1617
Examiner Name	S. PIHONAK
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA*	JP-2000-26292-A	01-25-2000			
	BB	EP-1327440-A1	07-16-2003	Sumitomo Pharma		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Makino, T., et al., "Importance of Gelatinization Degree of Starch Past Binder in Hardness and Disintegration Time of Tablets," Chem. Pharm. Bull., Vol 43, No 3, pp 514-116 (1995)	

Examiner Signature	/Sarah Pihonak/	Date Considered	11/13/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Birch, Stewart, Kolasch & Birch, LLP DRN/ll

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P./

11/919678

IAP05Rec'd PCT 31 OCT 2007

Used in Lieu of PTO/SB/08A/B
(Based on PTO 10-07 version)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	NEW
				Filing Date	October 31, 2007
				First Named Inventor	Kazuyuki FUJIHARA
(Use as many sheets as necessary)				Art Unit	N/A
				Examiner Name	Not Yet Assigned
Sheet	1	of	1	Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-2004/0028741-A1	02-12-2004	Fujihara	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO-02/24166-A1	03-28-2002			ABS
	BB	WO-2004/078173-A1	09-16-2004			ABS
	BC	JP-8-325146-A	12-10-1996			

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature	/Sarah Pihonak/	Date Considered	11/13/2009

Birch, Stewart, Kolasch & Birch, LLP

DRN//scp

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P./

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     FILE 'HCAPLUS' ENTERED AT 13:06:25 ON 12 NOV 2009
L1             1 S US 20090143404/PN

     FILE 'REGISTRY' ENTERED AT 13:07:00 ON 12 NOV 2009
L2             1 S 9005-25-8/RN
                 SET NOTICE 1 DISPLAY
                 SET NOTICE LOGIN DISPLAY

     FILE 'REGISTRY' ENTERED AT 13:07:49 ON 12 NOV 2009
L3             1 S 367514-87-2/RN

L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   367514-87-2  REGISTRY
CN   4,7-Methano-1H-isoindole-1,3(2H)-dione,
     2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-
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(CA
     INDEX NAME)
OTHER NAMES:
CN   2-[[(1R,2R)-2-[[4-(1,2-Benzoisothiazol-3-yl)-1-
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4,7-methano-
     1H-isoindole-1,3(2H)-dione
CN   Lurasidone
FS   STEREOSEARCH
MF   C28 H36 N4 O2 S
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, CA, CAPLUS, CASREACT, EMBASE,
IMSDRUGNEWS,
       IMSRESEARCH, IPA, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
DT.CA  CAplus document type:  Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP
(Preparation); PROC
       (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL
(Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  BIOL (Biological study); USES (Uses)

Absolute stereochemistry.
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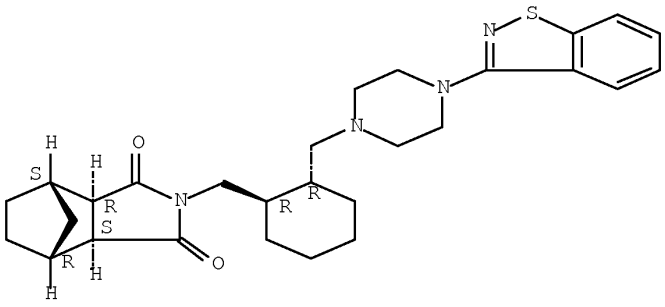

SET NOTICE 1 DISPLAY
SET NOTICE LOGIN DISPLAY

FILE 'HCAPLUS' ENTERED AT 13:08:02 ON 12 NOV 2009
L4 1 S L2 AND L3
L5 0 S L4 NOT L1
L6 3195 S L2 AND PHARMACEUTICAL TABLETS/IT
L7 227 S L6 AND (PY<2005 OR AY<2005 OR PRY<2005)
L8 9 S L7 AND PREGELATIN?

L8 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Tranexamic acid modified release oral formulations
AB Disclosed are modified release oral tranexamic acid formulations that preferably minimize or eliminate undesirable side effects and methods of treatment therewith. Thus, modified release 650 mg tranexamic acid tablets comprised (in mg/tablet): tranexamic acid 650.0, microcryst. cellulose 44.25, colloidal silicon dioxide 0.75, pregelatinized corn starch 49.50, hypromellose 147.00, povidone 36.00, stearic acid 18.00, magnesium stearate 4.50, purified water 135.00.

ACCESSION NUMBER: 2009:1016627 HCAPLUS Full-text
DOCUMENT NUMBER: 151:272936
TITLE: Tranexamic acid modified release oral formulations
INVENTOR(S): Moore, Keith A.; Heasley, Ralph A.; Greiwe, Jeffrey S.; Facemire, John W.; Modest, Jason D.
PATENT ASSIGNEE(S): Xanodyne Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 46pp., Cont.-in-part of U.S. Ser. No. 220,241.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090209646	A1	20090820	US 2009-433510	20090430 <--
US 20050245614	A1	20051103	US 2005-72162	

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20050304 <--
     WO 2006023000        A1    20060302    WO 2005-US20558
20050613 <--
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,
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              CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD,
              GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP,
KR, KZ,
              LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NA,
              NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
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              SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
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              CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
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              KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
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     WO 2006023001        A1    20060302    WO 2005-US20563
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VN, YU,
              ZA, ZM, ZW
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BY, KG,
              KZ, MD, RU, TJ, TM
     JP 2008508275        T     20080321    JP 2007-523555
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     JP 2008508276        T     20080321    JP 2007-523556
20050613 <--
     US 20080280981       A1    20081113    US 2008-220241
20080723 <--
PRIORITY APPLN. INFO.:                      US 2004-550113P     P
20040304 <--
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US 2004-592885P P
20040730 <--
US 2005-72162 B1
20050304
US 2008-220241 A2
20080723
WO 2005-US20558 W
20050613
WO 2005-US20563 W
20050613
INCL 514561000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Pharmaceutical tablets
(coated tablets; tranexamic acid modified release oral formulations)
IT Constipation
Diarrhea
Dissolution
Drug bioavailability
Drug bioequivalence
Headache
Human
Nausea
Oral drug delivery systems
Pharmaceutical capsules
Pharmaceutical granules
Pharmaceutical lozenges
Pharmaceutical pellets
Pharmaceutical powders
Pharmaceutical tablets
Pharmacokinetics
Vomiting
(tranexamic acid modified release oral formulations)
IT 57-11-4, Stearic Acid, biological studies 557-04-0, Magnesium Stearate
7631-86-9, Silicon Dioxide, biological studies 9003-39-8, Povidone
9004-34-6, Cellulose, biological studies 9004-65-3, Hypromellose
9005-25-8, Starch, biological studies 390816-70-3, Opadry White YS 1-7003
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(tranexamic acid modified release oral formulations)

L8 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Controlled release pharmaceutical compositions
AB A non-disintegrating, non-eroding, non-bioadhesive and non-swelling oral controlled-release pharmaceutical composition and process for preparation of such compns. is provided which comprises at least one high-dose water-soluble drug, a diluent, a binder, and a polymer system comprising of a release-controlling polymer wherein the composition formulated into a suitable dosage form maintains its geometric shape even after the drug has diffused from the dosage form and provides the concns. of active ingredient above effective levels for extended periods of time,

optionally with other excipients. The compns. preferably comprise antibiotic(s) as active ingredient, more preferably amoxicillin or its salts, hydrates, polymorphs, esters, and derivs. thereof, most preferably amoxicillin sodium, either alone or in combination with other antibiotic(s). Also described are controlled-release compns. which provide an initial burst release of approx. 20-40% of the active ingredient within 1 h for achieving blood levels equivalent to min. inhibitory concentration, while maintaining these levels for an extended period of time.

ACCESSION NUMBER: 2009:393268 HCAPLUS Full-text
DOCUMENT NUMBER: 150:383031
TITLE: Controlled release pharmaceutical compositions
INVENTOR(S): Jain, Rajesh; Jindal, Kour Chand; Singh, Sukhjeet
PATENT ASSIGNEE(S): Panacea Biotec Ltd., India
SOURCE: U.S. Pat. Appl. Publ., 9pp., Cont.-in-part of Appl.
No. PCT/IN2005/000004.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090088415	A1	20090402	US 2006-482185	20060706 <--
IN 2004DE00023	A	20060210	IN 2004-DE23	20040106 <--
WO 2005065641	A2	20050721	WO 2005-IN4	20050105 <--
WO 2005065641	A3	20060427		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SM				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
ZA 2006006408	A	20081126	ZA 2006-6408	20050105 <--

PRIORITY APPLN. INFO.: IN 2004-DE23 A
20040106 <--
IN 2004-DE28 A
20040106 <--
WO 2005-IN4 A2
20050105
INCL 514192000; 514200000; 514197000; 514356000
CC 63-6 (Pharmaceuticals)
IT Pharmaceutical capsules
Pharmaceutical granules
Pharmaceutical tablets
(controlled-release; controlled-release pharmaceutical compns.)
IT 9005-25-8, Starch, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pregelatinized; controlled-release pharmaceutical compns.)

L8 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Vitamin B12 and folic acid combinations for oral tablets
AB The invention concerns the preparation of solid oral combinations of vitamin B12 with folic acid or another vitamin B compds.; the vitamins are dissolved in suitable binding agents and then mixed with other components and auxiliary agents to form tablets. Thus a tablet mixture contained (kg): folic acid 0.228; cyanocobalamine 0.038; pyridoxine 1.9; pregelatinized corn starch 7.6; lactose monohydrate 7.6; cellulose 16.834; gelatin 1.52; water 9.88; talc 1.52; hydrogenated castor oil 0.76. Cyanocobalamine, folic acid and gelatin were completely dissolved in water prior adding the other components.
ACCESSION NUMBER: 2008:163501 HCAPLUS Full-text
DOCUMENT NUMBER: 148:175746
TITLE: Vitamin B12 and folic acid combinations for oral
tablets
INVENTOR(S): Scheiwe, Max Werner
PATENT ASSIGNEE(S): Mepha AG, Switz.
SOURCE: Patentschrift (Switz.), 9pp.
CODEN: SWXXAS
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CH 696870	A5	20080115	CH 2004-1319	
20040809 <--				
PRIORITY APPLN. INFO.:			CH 2004-1319	
20040809 <--				

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Dissolution
Fetal distress
Neurodegenerative disease
Oral drug delivery systems
Pharmaceutical capsules
Pharmaceutical films

Pharmaceutical granules
Pharmaceutical solids
Pharmaceutical tablets
Vascular disease
(vitamin B12 and folic acid combinations for oral tablets)
IT 50-99-7, D-Glucose, biological studies 59-30-3, Folic acid, biological
studies 68-19-9, Vitamin B12 1327-43-1, Magnesium aluminum silicate
9000-07-1, Carrageenan 9000-30-0, Guar gum 9000-65-1, Tragant gum
9003-39-8, Polyvinylpyrrolidone 9004-65-3, Hydroxypropylmethylcellulose
9005-25-8, Starch, biological studies 9050-36-6, Maltodextrin
9062-14-0, Hydroxypropylethylcellulose 12001-76-2, Vitamin B
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vitamin B12 and folic acid combinations for oral tablets)

L8 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Novel drug delivery systems for amoxicillin
AB A novel composition is disclosed of oral controlled release formulations of amoxycillin for releasing the drug over a prolonged period of time suitable for ones a day administration in highly absorptive regions of the gastrointestinal tract using dissoln. controlled matrix technol. Thus, tablets contained amoxicillin trihydrate 1148, starch 112, pregelatinized starch 90, hydroxypropyl Me cellulose K4M 120, talc 15, Mg stearate 15, and colloidal silica 7.5 mg/tablet.
ACCESSION NUMBER: 2007:179133 HCAPLUS Full-text
DOCUMENT NUMBER: 146:365585
TITLE: Novel drug delivery systems for amoxicillin
INVENTOR(S): Kesharlal, Biyani Milind; Khushikesh, Jathar Shripad;
Simha, Nanda Pratap
PATENT ASSIGNEE(S): Ajanta Pharma Ltd., India
SOURCE: Indian Pat. Appl., 23pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 1999BO00836	A	20050318	IN 1999-BO836 19991124 <--	

PRIORITY APPLN. INFO.: IN 1999-BO836 19991124 <--
IC ICM A61K007-00
CC 63-6 (Pharmaceuticals)
IT Pharmaceutical tablets
(controlled-release; drug delivery systems for amoxicillin)
IT 9003-39-8, Polyvinylpyrrolidone 9004-34-6D, Cellulose, derivs.
9004-57-3, Ethyl cellulose 9004-65-3, Hydroxypropyl methyl cellulose
9005-25-8, Starch, biological studies 9005-25-8D,

Starch, derivs. 26787-78-0, Amoxicillin 61336-70-7, Amoxicillin
trihydrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug delivery systems for amoxicillin)

L8 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Starch based excipients for pharmaceutical tablets
AB Starch and modified starches are safe and well established excipients and they can be phys. modified to enhance their properties to improve their performance, and could also be chemical modified to obtain a very wide range of new properties that can play an important role in the formulation of complex delivery systems. Tablets containing regular maize starch easily allow water to penetrate into the tablet, softening it for fast disintegration. Pregelatinized or cold water soluble starches act as strong binders leading to stronger, but also slower, disintegrating tablets. A direct compressible starch that has to be both a binder and a disintegrant needs to possess the correct ratio of both crystalline to amorphous structure. Slow-release tablets involve the encapsulation of an active ingredient in a modified starch matrix like a modified pregelatinized high amylose maize starch. The bioadhesive tablet, containing pregelatinized waxy starch is applied to increase buccal residence time of miconazole.

ACCESSION NUMBER: 2002:579348 HCAPLUS Full-text
DOCUMENT NUMBER: 138:243111
TITLE: Starch based excipients for pharmaceutical tablets
AUTHOR(S): Michaud, Jacques
CORPORATE SOURCE: Application Centre Pharma & Chemical, Cerestar,
Vilvoorde, Belg.
SOURCE: PharmaChem (2002), 1(6), 42-44
CODEN: PHARGZ
PUBLISHER: B5 srl
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 63-6 (Pharmaceuticals)
IT Drug delivery systems
(tablets; starch based excipients for pharmaceutical tablets)
IT 9005-25-8, Starch, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(starch based excipients for pharmaceutical tablets)
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Sustained-release pharmaceutical tablets containing combination of

piperidinoalkanols and decongestants

AB A pharmaceutical composition in the form of a bilayer tablet is provided comprising, (a) a first discrete zone made with formulation (A) which comprises, a therapeutically effective decongestant amount of a sympathomimetic drug, or a pharmaceutically acceptable salt thereof, in an amount of about 18% to about 39% by weight of formulation (A), and a first carrier base material, the first carrier base material comprising a mixture of; (i) carnauba wax in an amount of about 59% to about 81% by weight of formulation (A); and (ii) a suitable antiadherent in an amount of about 0.25% to about 2.00% by weight of formulation (A). Wherein said first carrier base material provides a sustained release of the sympathomimetic drug; and (b) a second discrete zone made with formulation (B) which comprises a therapeutically effective antihistaminic amount of a piperidinoalkanol, or a pharmaceutically acceptable salt thereof, in an amount of about 15% to about 30% by weight of formulation (B) and a second carrier base material, the second carrier base comprising a mixture of; (i) a cellulose diluent in an amount of about 27% to about 73% by weight of formulation (B); (ii) pregelatinized starch in an amount of about 15% to about 30% by weight of formulation (B); (iii) a suitable disintegrant in an amount of about 0.25% to about 6.00% by weight of formulation (B); and (iv) a suitable lubricant in an amount of about 0.25% to about 2.00% by weight of formulation (B); wherein said second carrier base material provides an immediate release of the piperidinoalkanol or the pharmaceutically acceptable salt thereof. A bilayer tablet contained 4[4[4(Hydroxydiphenylmethyl)-1-piperdinyl]-1-hydroxybutyl] dimethylbenzeneacetic acid hydrochloride 60.00, microcryst. cellulose 26.00, pregelatinized starch 60.00, microcryst. cellulose (Avicel PH 102) 190.5, croscarmellose sodium 12.00, magnesium stearate 2.633 mg in the immediate-release layer; pseudoephedrine hydrochloride 120.0, carnauba wax 300.0, stearic acid flakes 4.899, colloidal silicon dioxide 1.065, and Opadry YS-17006 23.31 mg in the sustained-release layer.

ACCESSION NUMBER: 2000:186719 HCAPLUS Full-text
DOCUMENT NUMBER: 132:227453
TITLE: Sustained-release pharmaceutical tablets containing combination of piperidinoalkanols and decongestants
INVENTOR(S): Maclaren, David D.; Lefler, John R.; Minish, Sharon K.
PATENT ASSIGNEE(S): Hoechst Marion Roussel, Inc., USA
SOURCE: U.S., 15 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6039974	A	20000321	US 1998-127478	19980731 <--

PRIORITY APPLN. INFO.: US 1997-90105 P 19970826 <--
IC ICM A61K009-22
ICS A61K009-24; A61K009-28
INCL 424472000
CC 63-6 (Pharmaceuticals)
IT Adrenoceptor agonists
Decongestants
Lubricants
(sustained-release pharmaceutical tablets containing combination of piperidinoalkanols and decongestants)
IT Carnauba wax
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release pharmaceutical tablets containing combination of piperidinoalkanols and decongestants)
IT Drug delivery systems
(tablets, sustained-release; sustained-release pharmaceutical tablets containing combination of piperidinoalkanols and decongestants)
IT 9005-25-8, Starch, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pregelatinized; sustained-release pharmaceutical tablets containing combination of piperidinoalkanols and decongestants)
IT 345-78-8, Pseudoephedrine hydrochloride 557-04-0, Magnesium stearate
7631-86-9, Silicon dioxide, biological studies 9004-34-6, Cellulose,
biological studies 74811-65-7, Croscarmellose sodium 153439-40-8
174523-28-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release pharmaceutical tablets containing combination of piperidinoalkanols and decongestants)
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD
(6 CITINGS)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Pharmaceutical tablets containing irbesartan
AB Pharmaceutical tablets containing irbesartan (I), alone or in combination with a diuretic, providing tablets with a high relative amount of active agent and excellent wetting and disintegration properties. Pharmaceutical tablets contained I 50, anhydrous lactose 10.25, pregelatinized starch 15.0, croscarmellose sodium 2.5, poloxamer-188 3.0, microcryst. cellulose 15.0, croscarmellose sodium 2.5, silicon dioxide 0.75, and magnesium stearate 1.0 %.
ACCESSION NUMBER: 1997:72239 HCAPLUS Full-text
DOCUMENT NUMBER: 126:94807
ORIGINAL REFERENCE NO.: 126:18213a,18216a
TITLE: Pharmaceutical tablets containing irbesartan
INVENTOR(S): Ku, Cathy C.; Sprockel, Omar L.; Rubitski,

Beth A.;
Desai, Divyakant S.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA; Sanofi Synthelabo
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 747050	A1	19961211	EP 1996-304291	19960607 <--
EP 747050	B1	20030903		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
TW 442301	B	20010623	TW 1996-85105820	19960516 <--
IL 118309	A	20030624	IL 1996-118309	19960517 <--
ZA 9604337	A	19971128	ZA 1996-4337	19960528 <--
CA 2177772	A1	19961208	CA 1996-2177772	19960530 <--
CA 2177772	C	20070410		
CZ 291532	B6	20030312	CZ 1996-1634	19960605 <--
NO 9602387	A	19961209	NO 1996-2387	19960606 <--
NO 310495	B1	20010716		
AU 9654763	A	19961219	AU 1996-54763	19960606 <--
AU 702651	B2	19990225		
HU 9601564	A2	19980928	HU 1996-1564	19960606 <--
HU 9601564	A3	20001228		
RU 2181590	C2	20020427	RU 1996-111030	19960606 <--
RU 2210368	C1	20030820	RU 2001-130903	19960606 <--
JP 08333253	A	19961217	JP 1996-145579	19960607 <--
JP 3162626	B2	20010508		
CN 1144656	A	19970312	CN 1996-106832	19960607 <--
CN 1149083	C	20040512		
EP 1275391	A1	20030115	EP 2002-16237	19960607 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PL 184893	B1	20030131	PL 1996-314670	19960607 <--

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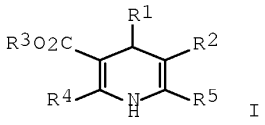
     AT 248594            T     20030915    AT 1996-304291
19960607 <--
     ES 2205000           T3    20040501    ES 1996-304291
19960607 <--
     HK 1002384           A1    20040305    HK 1998-100693
19980127 <--
     US 5994348           A     19991130    US 1998-81685
19980520 <--
     NO 2000004743        A     19961209    NO 2000-4743
20000922 <--
     NO 310393            B1    20010702
     US 6342247           B1    20020129    US 2000-686378
20001011 <--
PRIORITY APPLN. INFO.:                       US 1995-472618      A
19950607 <--
                                             US 1996-642978      B1
19960506 <--
                                             RU 1996-111030      A
19960606 <--
                                             EP 1996-304291      A3
19960607 <--
                                             US 1998-81685       A3
19980520 <--
                                             US 1999-390868      B1
19990907 <--
IC   ICM  A61K031-415
     ICS  A61K009-00; A61K009-20
CC   63-6 (Pharmaceuticals)
IT   Glycerides, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (C16-18; pharmaceutical tablets containing irbesartan)
IT   Diuretics
     Surfactants
        (pharmaceutical tablets containing irbesartan)
IT   Drug delivery systems
        (tablets; pharmaceutical tablets containing irbesartan)
IT   Fats and Glyceridic oils, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (vegetable, hydrogenated; pharmaceutical tablets
        containing irbesartan)
IT   9004-34-6, Cellulose, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (microcryst.; pharmaceutical tablets containing
        irbesartan)
IT   57-11-4, Stearic acid, biological studies   58-93-5,
Hydrochlorothiazide
     58-94-6, Chlorothiazide   63-42-3, Lactose   73-48-3,
Bendroflumethiazide
     73-49-4, Quinethazone   77-36-1, Chlorthalidone   91-33-8,
Benzthiazide
     133-67-5, Trichlormethiazide   135-09-1, Hydroflumethiazide   346-
18-9,
     Polythiazide   532-32-1, Sodium benzoate   557-04-0, Magnesium
stearate
     557-05-1, Zinc stearate   1592-23-0, Calcium stearate   2259-96-3,
     Cyclothiazide   4070-80-8, Sodium stearyl fumarate   7631-86-9,
Silicon
```

dioxide, biological studies 7757-93-9, Dibasic calcium phosphate
9003-39-8, Povidone 9004-32-4, Carboxymethyl cellulose sodium
9004-57-3, Ethyl cellulose 9004-62-0, Hydroxyethyl cellulose
9004-64-2, Hydroxypropyl cellulose 9004-65-3,
Hydroxypropylmethyl
cellulose 9004-67-5, Methyl cellulose 9005-25-8, Starch,
biological studies 9005-32-7, Alginic acid 9005-38-3, Sodium
alginate
14807-96-6, Talc, biological studies 14987-04-3, Magnesium
trisilicate
17560-51-9, Metolazone 25322-68-3, Peg 31566-31-1, Glyceryl
monostearate 64044-51-5, Lactose monohydrate 106392-12-5,
Poloxamer
138402-11-6, Irbesartan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical tablets containing irbesartan)
IT 1309-37-1, Ferric oxide, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(red and yellow; pharmaceutical tablets containing
irbesartan)
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE
THIS
RECORD (16 CITINGS)

L8 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Retarded-release pharmaceuticals containing dihydropyridines as
active
agents and having rapid-release cores and slowly dissolving
coatings
GI



I

AB Solid pharmaceutical formulations with a prolonged efficacy
contain a dihydropyridinecarboxylate derivative (I; R1 = nitro-,
halo-, or CF3-mono- or disubstituted Ph, benzofuran-4-yl,
2-phenyl-4-oxo-4H-1-benzothiopyran-8-yl; R2 = NO2, CO2R6; R3 =
optionally alkoxy- or F-substituted alkyl; R4, R5 = optionally OH-
substituted alkyl; R2R5 = CO2CH2; R6 = optionally alkoxy- or halo-
substituted alkyl). The pharmaceutical consists of a core which
is capable of rapidly releasing ≥1 I; the cores are coated with a
coating, free of active agent, which only slowly dissolves in
aqueous medium. The coating optionally carries a coating which is
capable of rapidly releasing an initial dose of dihydropyridine;
the diameter of the formulations is 0.5-15 mm. Tablet cores
containing microfine nitrendipine 8.0, lactose 8.0, microcryst.
cellulose 8.0, crosslinked PVP 16.0, PVP-25 4.0, SDS 0.8, and Mg
stearate 0.2 mg each were coated to contain in their coatings

hydroxypropylcellulose (type L) 50.0, hydroxypropylcellulose (type M) 87.5, lactose 110.0, and Mg stearate 1.65 mg each. A lacquer rapid-release coating was applied to these coated tablets which contained nitrendipine 4.0, hydroxypropylmethylcellulose, and PEG. The tablets thus gave a retarded-release effect.

ACCESSION NUMBER: 1989:639511 HCAPLUS Full-text
DOCUMENT NUMBER: 111:239511
ORIGINAL REFERENCE NO.: 111:39663a,39666a
TITLE: Retarded-release pharmaceuticals containing dihydropyridines as active agents and having rapid-release cores and slowly dissolving coatings
INVENTOR(S): Ohm, Andreas; Luchtenberg, Helmut; Buecheler, Manfred; Schmoll, Josef; Rupp, Roland; Porges, Eduard; Nishioka, Takaaki
PATENT ASSIGNEE(S): Bayer A.-G., Fed. Rep. Ger.
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 306699	A1	19890315	EP 1988-112494	19880801 <--
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DE 3726666	A1	19890223	DE 1987-3726666	19870811 <--
DE 3810350	A1	19891005	DE 1988-3810350	19880326 <--

PRIORITY APPLN. INFO.: DE 1987-3726666 A 19870811 <--
DE 1988-3810350 A 19880326 <--
OTHER SOURCE(S): MARPAT 111:239511
IC ICM A61K031-44
ICS A61K009-24; A61K009-54
CC 63-6 (Pharmaceuticals)
IT 9005-25-8, Starch, biological studies
RL: BIOL (Biological study)
(pregelatinized, retarded-release pharmaceuticals containing dihydropyridine-containing rapid-release core and coating of)
IT 39562-70-4, Nitrendipine
RL: BIOL (Biological study)
(retarded-release pharmaceutical tablets of, containing rapid-release core and slowly dissolving coating)
IT 9003-39-8, Poly(vinylpyrrolidinone)
RL: BIOL (Biological study)
(retarded-release pharmaceutical tablets with slowly dissolving coating and rapid-release core containing)
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD
(2 CITINGS)

L8 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
TI Spray-dried ibuprofen-containing powders for direct-impression tabletting
applications
AB Spray-dried ibuprofen compns. are suitable for direct compression into tablets and consist essentially of spray-dried aqueous dispersions of ibuprofen, preglatinized starch, a disintegrant, and a wetting agent for ibuprofen. In a semiprodn. run, a dry blend containing pregelatinized starch 10.25, croscarmellose Na 3.50, colloidal silica 0.25, povidone 1.00, and ibuprofen 85.00% was used to prepare a 30% aqueous dispersion of solids in 246 gal H2O which was fed into a spray dryer; the spray dryer was operated at an air inlet temperature of 270-275°F and an air outlet temperature of 140°F, the atomizer at 18,639 rotations/min, and a feed rate of 0.77-0.87 gal/min. Tablets contained the spray-dried powder above 236.0 pregelatinized starch 22.5, compressible starch 22.5, croscarmellose Na (type A) 18.0, colloidal silica 0.45, Na lauryl sulfate 0.75, and stearic acid 1.80 mg/tablet.
ACCESSION NUMBER: 1989:520917 HCAPLUS Full-text
DOCUMENT NUMBER: 111:120917
ORIGINAL REFERENCE NO.: 111:20153a,20156a
TITLE: Spray-dried ibuprofen-containing powders for direct-impression tabletting applications
INVENTOR(S): Ho, Ying Tien Richard; Blank, Robert George
PATENT ASSIGNEE(S): American Home Products Corp., USA
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 298666	A2	19890111	EP 1988-306003	19880701 <--
EP 298666	A3	19890517		
EP 298666	B1	19930811		
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL				
AT 92752	T	19930815	AT 1988-306003	19880701 <--
ES 2058288	T3	19941101	ES 1988-306003	19880701 <--
CA 1319109	C	19930615	CA 1989-588463	19890117 <--
US 4904477	A	19900227	US 1989-378480	19890713 <--
PRIORITY APPLN. INFO.:			US 1987-71116 A	19870708 <--
			EP 1988-306003 A	19880701 <--

IC ICM A61K009-20
ICS A61K031-19; A61K047-00
CC 63-6 (Pharmaceuticals)
IT 15687-27-1, Ibuprofen

RL: BIOL (Biological study)
(direct compressed pharmaceutical tablets containing)
IT 151-21-3, Sodium lauryl sulfate, biological studies 9003-39-8, Povidone
9005-25-8, Starch, biological studies 9063-38-1, Sodium starch glycolate 74811-65-7, Croscarmellose sodium
RL: BIOL (Biological study)
(direct compressed pharmaceutical tablets containing ibuprofen and)

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11919678
Filing Date	2007-10-31
First Named Inventor	Kazuyuki FUJIHARA
Title	Pharmaceutical Composition
Art Unit	1627
Examiner Name	Pihonak, Sarah
Attorney Docket Number	7379/98100

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: **42798**

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature		Date	March 26, 2010
Name	Masayo TADA	Telephone	
Title and Company	President and Representative Director of Dainippon Sumitomo Pharma Co.,Ltd		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Kazuyuki FUJIHARA

Application No./Patent No.: 11919678 Filed/Issue Date: 2007-10-31

Titled: Pharmaceutical Composition

Dainippon Sumitomo Pharma Co., Ltd. , a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 020124, Frame 0821, or for which a copy therefore is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[X] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — March 26, 2010 (Date)

Masayo TADA (Printed or Typed Name)

President and ~~Representative Director~~ (Title)

Electronic Acknowledgement Receipt

EFS ID:	7561094
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	02292
Filer:	Kendrew H. Colton
Filer Authorized By:	
Attorney Docket Number:	0020-5610PUS1
Receipt Date:	06-MAY-2010
Filing Date:	31-OCT-2007
Time Stamp:	10:08:46
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	PowerAttorney.pdf	113437 f3ed5bfdc6b715d06b98db6441b55be4a0fd6a39	no	1

Warnings:	
Information:	

2	Power of Attorney	Statement.pdf	97015 79ae2cd9937e6f5cf5c7cf01f24659c4d3ad16ee	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	210452

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/919,678	10/31/2007	Kazuyuki Fujihara	7379/98100

CONFIRMATION NO. 6965

POA ACCEPTANCE LETTER

42798
FITCH, EVEN, TABIN & FLANNERY
P. O. BOX 18415
WASHINGTON, DC 20036

OC000000041587393

Date Mailed: 05/13/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/06/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/sleutchit/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/919,678	10/31/2007	Kazuyuki Fujihara	0020-5610PUS1

CONFIRMATION NO. 6965

POWER OF ATTORNEY NOTICE

2292
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

OC000000041587333

Date Mailed: 05/13/2010

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/06/2010.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/sleutchit/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Attorney Docket No.: 7379/98100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:		
	:		
Kazuyuki FUJIHARA	:	Confirmation No.:	6965
	:		
U.S. Application No.: 11/919,678	:	Examiner:	PIHONAK, SARAH
	:		
Filed: October 31, 2007	:	Group Art Unit:	1627
	:		

For: PHARMACEUTICAL COMPOSITION

AMENDMENT

May 24, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Kindly enter this Amendment and grant the concurrently filed Petition for Extension of Time.

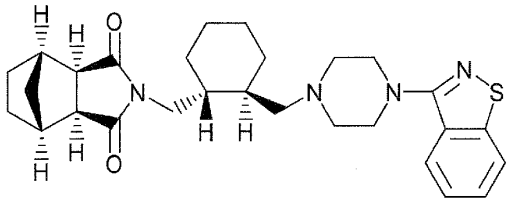
1. **Amendments to Claims** begin on page 2 of this paper.
2. **Remarks/Arguments** begin on page 7 of this paper.

Amendments to the Claims:

This listing of claims replaces any and all prior claim lists.

Listing of Claims:

1. (Currently Amended) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

2. (Currently Amended) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

3. (Currently Amended) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder;

wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

4. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose.

5. (Withdrawn – Currently Amended) A method ~~of~~ for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

6. (Withdrawn – Currently Amended) A method ~~of~~ for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by using a solution or dispersion of lurasidone and a water-soluble polymer binder.

7. (Withdrawn – Currently Amended) The method ~~of granulation~~ of claim 5 wherein the water-soluble excipient is mannitol or lactose.

8. **(Cancelled)**

9. (Previously presented) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10. **(Cancelled)**

11. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

12. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. **(Cancelled)**

16. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17. **(Cancelled)**

18. **(Cancelled)**

19. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount

of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

20. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Previously Presented) The oral preparation of claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Previously Presented) The oral preparation of claim 1 wherein an average particle size of lurasidone is 0.1 to 8 μm.

23. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content lurasidone per tablet is 20 to 120 mg.

25. (New) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 20 to 45% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

26. (New) The oral preparation of claim 9 wherein the water-soluble excipient is mannitol or lactose.

REMARKS

Applicants courteously solicit favorable reconsideration followed by a Notice of Allowance.

Upon entry of this Amendment claims 1-7, 9, 11-14, 16, and 19-26 will be presented. Claims 8, 15, 16, and 18 have been cancelled with neither prejudice nor disclaimer. Claim 1 includes language drawn from claims 10 and 15. Similarly, claims 2 and 3 have been amended. Amended non-elected claims 5, 6, and 7 find basis in the original application, and attention is respectfully invited to the examples. New claims 25 and 26 are supported, respectively, by the original claims 10 and 24 and original claim 9. The amended and new claims avoid new matter and entry thereof is courteously solicited.

Applicants acknowledge the Office Action at page 2 and respectfully solicit allowance of the group I claims, and rejoinder of the withdrawn method claims 5-7 is also requested. Applicants notes the rejoinder offered in the Office Action, page 2, paragraph 2.

Traversal of Rejection under 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 1-4 and 8-24 under 35 U.S.C. §103(a) over Fujihara *et al.* (EP Patent Publication No. 1327440) in view of Salpekar *et al.* (U.S. Patent No. 4,600,579).

By way of background, aspects of the present claimed inventions involve an oral preparation that may comprise high contents of a hardly-soluble pharmaceutically active agent (e.g. lurasidone), yet the preparation exhibits a similar dissolution profile as compared to oral preparations having different contents of such pharmaceutically active agent (*see* paragraph [0013]). An aspect of the present invention includes an oral preparation having pregelatinized starch in the amount of 10-50% wt/wt per oral preparation.

The claims would not have been obvious over Fujihara *et al.* in view of Salpekar *et al.*

Although Fujihara discloses an oral composition comprising lurasidone which provides dissolution characteristics, Fujihara's 16.3% (wt/wt) or less of lurasidone is definitely different from the currently claimed invention in the content rates of lurasidone per oral preparation. This difference is one of the distinguishing aspects of the present claimed of the invention.

Fujihara only discloses that tablets comprising 8.13-16.3% (wt/wt) of lurasidone may have advantageous dissolution characteristics, and does not teach that any tablets comprising more than 16.3% (wt/wt) of lurasidone show remarkable dissolution profiles. In this respect, Fujihara's tablets of Comparative Examples 1-3, including a tablet comprising 29% of lurasidone (Comparative Example 3), are significantly inferior to the corresponding FC tablets of Examples 2-28 which comprise 8.13-16.3% (wt/wt) of lurasidone in terms of the dissolution characteristics (see [0185], [0191] and [0197]). Fujihara thus teaches away. Accordingly, Fujihara neither discloses nor suggests the claim 1 oral preparation comprising high amounts (20-45% (wt/wt)) of lurasidone which shows excellent dissolution profiles.

Furthermore, Fujihara's method does not yield (allow) compositions having high contents of lurasidone to show excellent dissolution profiles. As clearly disclosed in Test 1 (Tables 1-5, Figure 2 and Comparative Examples 1 and 2) of the original description, two tablets of Comparative Example 1 and 2 were prepared according to Fujihara's method and comprised lurasidone in the weight of 12.3% and 24.7%, respectively. Test 1 shows that Fujihara's tablet comprising 24.7% of lurasidone (80 mg tablet) clearly shows lower dissolution profile than that comprising 12.3% of lurasidone in 15 minutes (see Figure 2, Table 4, [0039]). In contrast, the present oral preparation has favorable dissolution rates and similar dissolution profiles between tablets (see Test 1, Figure 3,

Tables 1-3, 13). As shown in Figure 3, dissolution rates of three tablets are more than 80% in 15 minutes. Table 4 and Figure 3 show that these tablets have similar dissolution profiles.

Whereas Fujihara does not disclose compositions comprising more than 16.3% (wt/wt) of lurasidone which show advantageous dissolution profiles as it only discloses those comprising 16.3% (wt/wt) or less of lurasidone, the instant invention provides a composition comprising 20% (wt/wt) or more of lurasidone which shows a remarkably advantageous dissolution profile. The advantageous dissolution profiles for the high content rates of lurasidone may result from inclusion of the recited amount of pregelatinized starch, which is not taught or suggested by Fujihara.

Fujihara's shortcomings are not overcome, even if, for the sake of argument it were combined with Salpekar *et al.*

Although Salpekar *et al.* teaches a composition comprised of a pharmaceutically active ingredient and pregelatinized starch, and even if arguendo some of such compositions may allow short dissolution time and shorter the dissolution and disintegration time, as the Examiner postulates, Salpekar *et al.* nonetheless does not provide any motivation towards the claimed inventions.

Specifically, the pharmaceutically active ingredient used by Salpekar *et al.* is N-acetyl-p-aminophenol (Acetaminophen) (see lines 6-14 of column 1). According to DrugBank (http://www.drugbank.ca/drugs/DB00316), the experimental water solubility of acetaminophen is 14 mg/mL (see the attachment). In contrast, the water solubility of lurasidone is 0.224 mg/mL at 20°C which is extremely lower (approximately 1/62.5) than that of acetaminophen.

That means that lurasidone is much more difficult from the solubility standpoint than acetaminophen, and that Salpekar *et al.* just relates to a comparatively soluble agent "acetaminophen," not to a hardly-soluble agent.

In addition, Salpekar *et al.* discloses that a preferred embodiment is a composition comprising 93-83% of acetaminophen (see line 63, column 5 to line 9, column 6). Those skilled in the art cannot apply Salpekar's formulation for comparatively soluble agents including extremely high contents (93-83%) of the active ingredient to tablets comprising a hardly-soluble lurasidone in order to solve the problem of the undesired dissolution profiles of hardly-soluble agents in any conventional compositions. The higher contents of the different material teach away from the claim 1 oral preparation. Therefore, Applicants submit a combination of Salpekar *et al.* with Fujihara is proscribed hindsight.

Even if, for the sake of argument, Salpekar *et al.* were combined with Fujihara, a person skilled in the art cannot arrive at the inventive content rates of pre gelatinized starch (10 to 50% (wt/wt)) as below. Although Salpekar *et al.* teaches that effective amount of PGS (i.e., pregelatinized starch) is from about 5 or less to about 15 or more parts per 100 parts of the composition (see lines 15-17 of column 4), Salpekar's compositions which substantially show significant technical effects are only those supported by Examples (i.e., 4.45-8.85% of PGS), in view of Salpekar's disclosure that the PGS is included in an amount effective for imparting to the composition the capability of being formed into tablets having high hardness, short disintegration time (e.g., about 10 minutes or less) and short dissolution time (e.g., about 20 minutes or less for 80% or more of the APAP to dissolve) (see lines 3-9 of column 4).

As seen from Table of column 8 and taken lines 3-9 of column 4 into consideration, Ex.1 tablet (18.0% of PGS) is not acceptable in order to solve Salpekar's problem, since the disintegration time of Ex. 1 tablet is 18.0 minutes which is 3-12 times longer than that of Ex. 2 (6 minutes) or Ex.3 tablet (1.5 minutes). Even Ex.2 tablet comprising 8.85% of PGS is not perfectly acceptable in terms of 4-times longer disintegration time than Ex.3 tablet.

Therefore, those skilled in the art may understand that 4.45-8.85% of PGS is preferable for a tablet having a short disintegration time and a short dissolution time. Accordingly, a person of ordinary skill in the art cannot arrive at pregelatinized starch (10 to 50% (wt/wt)), beyond Salpekar's preferable ranges, which can cause compositions comprising high content rates of the active ingredient with the advantageous dissolution profiles.

Conclusion

Applicant has found that it is possible to provide an oral preparation which includes a high concentration of lurasidone (20 to 45 wt.-%) in combination with 10 to 50 wt.-% pregelatinized starch that provides advantageous dissolution profiles. None of the prior art documents, alone or in combination, would have taught or suggested this combination of features or that the advantages can be achieved therewith.

In view of the above amendment and remarks, Applicant respectfully request favorable reconsideration of the instant application in the form of a Notice of Allowance.

If the Examiner has any questions concerning the application, or perhaps suggestions for further constructively advancing patent prosecution, kindly contact Applicants' undersigned representative.

Applicants hereby request that any concurrent or future reply submitted by Applicants to the U.S. Patent and Trademark Office in connection with the above-identified patent application requiring an extension of time under 37 C.F.R. §1.136(a) for its timely submission be treated as incorporating therein a request for an extension of time for the appropriate length of time. In addition, to the extent necessary during prosecution of the present application, Applicants hereby authorize the Commissioner to charge any required fee not otherwise provided for, including application processing, extension, and extra claims fees, to Deposit Account No. 06-1135 with reference to Attorney Docket No. **7379/98100**.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

/Kendrew H. Colton/

Kendrew H. Colton
Registration No. 30,368

Please send official correspondence to:

FITCH, EVEN, TABIN & FLANNERY
1120 20th St., NW, Suite 750 South
Washington, DC 20036
Tel: (202) 419-7000
Fax: (202) 419-7007
Customer Number 42798

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** (*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*)	Docket Number (Optional) 7379/98100
Application Number 11/919,678	Filed October 31, 2007
For Pharmaceutical Composition	
Art Unit 1627	Examiner Pihonak, Sarah

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$130	$65	$
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☑ Three months (37 CFR 1.17(a)(3))	$1110	$555	$ 1110.00
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 061135.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 30368

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Kendrew H. Colton/ — Signature

May 24, 2010 — Date

Kendrew H. Colton — Typed or printed name

202-419-7000 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	11919678
Filing Date:	31-Oct-2007
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Filer:	Kendrew H. Colton/Kindra Johnson
Attorney Docket Number:	7379/98100

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**1110**

Electronic Acknowledgement Receipt	
EFS ID:	7673443
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	42798
Filer:	Kendrew H. Colton/Kindra Johnson
Filer Authorized By:	Kendrew H. Colton
Attorney Docket Number:	7379/98100
Receipt Date:	24-MAY-2010
Filing Date:	31-OCT-2007
Time Stamp:	15:46:52
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1110
RAM confirmation Number	2293
Deposit Account	061135
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2010-05-24--Amendment.pdf	143086 faede9e0a1f5aede383262fa328360b98f78258b	yes	12
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	12	
Warnings:					
Information:					
2	Extension of Time	2010-05-24--EOT.pdf	321940 fed9135eb6e22f40cc8c2f8200e40d38d5e94316	no	2
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	29881 367f743de4da03d217487465573410d7928709c3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	494907		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/919,678	10/31/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 05/24/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 24	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***5	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANGELONA D. JONES/

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	7379/98100	6965

42798 7590 07/27/2010

FITCH, EVEN, TABIN & FLANNERY
P. O. BOX 18415
WASHINGTON, DC 20036

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
07/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/919,678	FUJIHARA, KAZUYUKI	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-14,16 and 19-26* is/are pending in the application.

4a) Of the above claim(s) *5-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,11-14,16 and 19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application, filed 10/31/2007, is a national stage entry of PCT/JP2006/310571, filed on 5/26/2006.

Priority

This application claims foreign priority to Application No. 2005-153508, filed on 5/26/2005.

Response to Remarks

1. Claims 8, 10, 15, 17-18 have been cancelled by the Applicants in the amendments filed on 5/24/2010; therefore, all rejections regarding these claims are rendered moot. Claims 5-7 were previously withdrawn from consideration, as being directed to a non-elected invention. New claims 25-26 have been added by the Applicants, and have been examined in this office action.

2. Applicant's arguments filed 5/24/2010 have been fully considered but they are not persuasive. The Applicants have argued that the claims would not have been prima facie obvious to one of ordinary skill in the art, at the time of the invention, over Fujihara et. al. in view of Salpekar et. al., because Fujihara et. al. does not teach that oral compositions comprised of 20-45% of lurasidone have improved dissolution profiles. The Applicants have asserted that Fujihara et. al. shows that a tablet comprised of 24.7% lurasidone has a lower dissolution profile than a tablet comprising 12.3% of lurasidone, and as such, one of ordinary skill in the art would not have been motivated to prepare the claimed oral preparation comprising 20 to 45% lurasidone. The examiner

respectfully disagrees. Fujihara et. al. teaches an oral composition comprised of lurasidone, in an amount up to 28% of the weight of the composition, along with disintegrants and a water soluble polymer binder. While Fujihara et. al. does not teach that the composition comprises pregelatinized starch, Salpekar et. al. teaches that pregelatinized starch is beneficial in oral pharmaceutical preparations for decreasing the dissolution and disintegration times, and imparting hardness to tablets. Therefore, as lurasidone is taught as a slightly water soluble active agent, and pregelatinized starch is taught to decrease the dissolution and disintegration times of oral formulations, one of ordinary skill in the art, at the time of the invention, would have been motivated to add pregelatinized starch to the composition comprised of lurasidone, within the weight percent range as claimed, to decrease the dissolution and disintegration profiles of lurasidone. The Applicants have asserted that Fujihara et. al. teaches that tablets comprised of higher amounts of lurasidone (24 %) have poorer dissolution profiles in comparison to formulations with lower amounts of lurasidone (12.3 %), one of ordinary skill in the art would not have been motivated to prepare an oral formulation with lurasidone in the amount range as claimed. This argument is not found persuasive, as Fujihara et. al. teaches oral compositions comprised of lurasidone in amounts up to 28% of the composition. While it is acknowledged that the formulation of lurasidone in an amount of 24.7% has a poorer dissolution profile in comparison to tablets comprising lower amounts of the drug, Salpekar et. al. teaches that pregelatinized starch improves the dissolution profiles of oral formulations. As such, it would have been prima facie

obvious to add pregelatinized starch to tablets comprising up to 28% of lurasidone to improve the dissolution and disintegration times.

The Applicants have asserted it would not have been prima facie obvious to combine the teachings of Salpekar with the teachings of Fujihara et. al., because the drug present in the oral formulation taught by Salpekar et. al. is more water soluble than lurasidone, as well as the amount of active drug in the composition taught by Salpekar et. al. is considerably greater than the amount of lurasidone instantly claimed. The examiner respectfully disagrees. Fujihara et. al. teaches that oral formulations of lurasidone up to 28% by weight can be prepared; Salpekar et. al. teaches that pregelatinized starch, in amounts ranging from 5 or less to 15 or more parts per 100 parts of the composition, improves dissolution and disintegration times. Therefore, as it is taught by Salpekar et. al. that pregelatinized starch can be used to improve the dissolution profile of an oral formulation comprised of a pharmaceutical agent, one of ordinary skill in the art would have been motivated to add pregelatinized starch, in the amount range as taught, to improve the dissolution profile of oral formulations comprised of other pharmaceutical agents, such as lurasidone. As Salpekar et. al. teaches that pregelatinized starch, within the weight percent range as claimed, improves the dissolution and disintegration properties of oral pharmaceutical formulations, one of ordinary skill in the art would have expected that the addition of pregelatinized starch to oral formulations comprised of lurasidone would also have resulted in improved dissolution and disintegration profiles. The rejection under 35 USC 103(a) was proper and is maintained, for reasons of record. For Applicants'

convenience, this rejection will be reiterated below, with slight modification due to new claims 25 and 26. Accordingly, this action is made FINAL.

3. Claims 1-4, 9, 11-14, 16, and 19-26 were examined.

4. Claims 1-4, 9, 11-14, 16, and 19-26 are rejected.

Claim Rejections-35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-4, 9, 11-14, 16, and 19-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujihara et. al., EP Patent Publication No. 1327440, in view of Salpekar et. al., US Patent No. 4,600,579 (both of previous record).

The claims are drawn to an oral composition comprised of lurasidone, pregelatinized starch, a water soluble excipient such as mannitol or lactose, and a water soluble polymer binder. The claims are also drawn to the composition in which the

pregelatinized starch is present in an amount from 10-50% by weight, and in which the lurasidone is present in an amount from 25 to 45% by weight.

Fujihara et. al. teaches an oral composition comprised of a slightly water soluble active ingredient, such as lurasidone, along with a first disintegrant, a second disintegrant, and a water soluble polymer binder (Abstract; p. 4-5, paragraph [0008]). Fujihara et. al. teaches that the composition provides advantageous dissolution characteristics when ingested (Abstract). It is taught that one of the water soluble excipients includes sugar alcohols such as mannitol or lactose (p. 3, paragraph [0017], item (18); p. 5, paragraph [0014]). The other disintegrant is taught as including excipients such as microcrystalline cellulose, croscarmellose sodium, among others (p. 5, paragraph [0011]), and the water soluble polymer binder includes polyvinylpyrrolidone, polyvinyl alcohol, and others (p. 5, paragraph [0010]). It is taught that the amount of lurasidone present in the oral composition is 40 mg., which is within the range instantly claimed (p. 5, paragraph [0015]; p. 22, paragraph [0152], Table 28), and that the average particle size of lurasidone is between 0.5 to 5 μm (p. 6, paragraph [0021]). It is taught that for a tablet of a weight of approximately 142 mg., the amount of lurasidone present is 40 mg., which is approximately 28 % of the weight of the composition (p. 29, paragraph [0194], Table 44). The amount of the disintegrants present in the composition is taught as ranging from 5 to 300 % by weight of the composition (p. 4, paragraph [0007], item (33)), or up to 1200% by weight (p. 6, paragraph [0029]). It is taught that the oral preparation comprises a granule, which is prepared by granulating the water-soluble polymer binder with the powdery mixture

consisting of the active agent (lurasidone), a water soluble excipient, and another disintegrant (p. 3, paragraph [0007], items (11-13); p. 4, paragraph [0007], item (40)). Fujihara et. al. teaches that the preparation can be formulated as pills, granules, fine granules, capsules, tablets, etc. (p. 5, paragraph [0016]).

Fujihara et. al. does not explicitly teach that the composition comprises pregelatinized starch, in an amount from 10 to 50% by weight of the composition.

Salpekar et. al. teaches a composition comprised of a pharmaceutically active ingredient, a lubricant, a disintegrant, and pregelatinized starch allows for high hardness, and short dissolution time when ingested (Abstract). Salpekar et. al. teaches that the composition comprised of the pregelatinized starch is beneficial for preparing oral pharmaceutical formulations such as tablets (column 1, lines 22-29). It is taught that the partially pregelatinized starch, such as the starch commercially known as Starch 1500, acts as a binder to the composition, and provides beneficial disintegrant properties, as well as increasing hardness of the composition and shortening the dissolution and disintegration time (column 3, lines 38-51; column 4, lines 31-37). Salpekar et. al. teaches that the amount of partially pregelatinized starch ranges from 5 or less to 15 or more parts per 100 parts of the composition (column 4, lines 15-17), which is within the amount of pregelatinized starch instantly claimed. It is taught that the amount of pregelatinized starch present is based upon the amount necessary to impart the high hardness and decreased dissolution times to the composition (column 4, lines 3-9); therefore, it would have been obvious to one of ordinary skill in the art that the optimum range of the pregelatinized starch may comprise amounts greater than or less

than 5-15 % by weight, as taught. Salpekar et. al. teaches that the percent gelatinization of the pregelatinized starch ranges optimally from 50 to 75% (column 2, lines 33-55). Additionally, it is taught that Starch 1500 has a moisture content between 3 and 5 % (column 3, lines 38-45).

One of ordinary skill in the art would have been motivated, at the time of the invention, to prepare the oral lurasidone preparation taught by Fujihara et. al. with the pregelatinized starch excipient taught by Salpekar et. al. because Salpekar et. al. teaches that the pregelatinized starch in oral pharmaceutical formulations provides beneficial properties, such as increased hardness of the tablet, decreased dissolution time after ingestion, and short disintegration time. As such, it would have been prima facie obvious for one of ordinary skill in the art to prepare the oral lurasidone composition as taught by Fujihara et. al. with the pregelatinized starch excipient as taught by Salpekar et. al. because both Fujihara et. al. and Salpekar et. al. teach pharmaceutical compositions formulated for oral administration. Therefore, there would have been an expectation of success in utilizing the pregelatinized excipient for the composition comprising lurasidone, because it is taught by Salpekar et. al. that the pregelatinized starch imparts beneficial properties to oral formulations.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search in EAST, PALM	11/12/2009	S.P.
Invention and claims search in EAST, STN	11/12/2009	S.P.
Inventor search in EAST, PALM	7/12/2010	S.P.
Invention and claims search in EAST, STN	7/12/2010	S.P.

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/S. P./ Examiner.Art Unit 1627	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/13/2009	07/20/2010							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	N	N							
	6	N	N							
	7	N	N							
	8	✓	-							
	9	✓	✓							
	10	✓	-							
	11	✓	✓							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							
	15	✓	-							
	16	✓	✓							
	17	✓	-							
	18	✓	-							
	19	✓	✓							
	20	✓	✓							
	21	✓	✓							
	22	✓	✓							
	23	✓	✓							
	24	✓	✓							
	25		✓							
	26		✓							

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2010/07/20 12:22
L2	4	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:23
L3	84	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:24
L4	15801	pregelatin$5 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:25
L5	31	l3 and l4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:25
L6	23548	accugel or absorbo or actobody or alphajel or allbond or alstar or amaizo or amalean or amerikor or amicoa or amidex or amigel or amilofax or amilys or amisol or amycol or amylex or amylogel or amylogum or amylomaize or amylon or amylose	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:27
L7	0	l3 and l6	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:28
S1	4	"2001076557".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2009/07/17 07:52
S2	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:53
S3	2622	pre-gelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54

EAST Search History (Prior Art)

S4	0	S2 and S3	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S5	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S6	25	S2 and S5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:55
S7	234938	oral and pharmaceutical	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S8	10067	S5 and S7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S9	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S10	446	S9 and oral	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:02
S11	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:17
S12	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S13	1	S11 and S12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18

EAST Search History (Prior Art)

S14	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S15	86	S11 and S14	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S16	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:57
S17	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S18	86	S16 and S17	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S19	1	"3607394".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2009/11/12 14:11
S20	67	(pregelatin$4 with starch) same (polymer with binder)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:29
S21	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S22	745	S21 and (starch adj "1500")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S23	47786	water adj solub$4 adj polymer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40

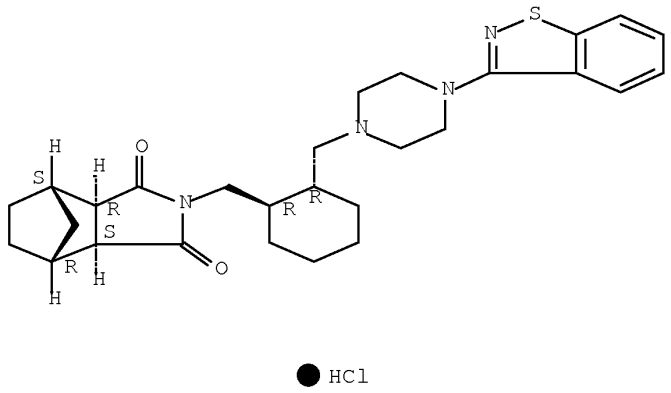
EAST Search History (Prior Art)

S24	43	S22 and S23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40
S25	99	S21 and (PCS)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:42
S26	5	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2009/11/12 15:05
S27	4	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2009/11/12 15:07
S28	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S29	1747	S28 and (water or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S30	202	S28 with (water or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:15

E LURASIDONE/CN

L1 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2010 ACS on STN
RN 367514-88-3 REGISTRY
ED Entered STN: 07 Nov 2001
CN 4,7-Methano-1H-isoindole-1,3(2H)-dione,
2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-
piperazinyl]methyl]cyclohexyl]methyl]hexahydro-, hydrochloride
(1:1),
(3aR,4S,7R,7aS)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4,7-Methano-1H-isoindole-1,3(2H)-dione,
2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-
piperazinyl]methyl]cyclohexyl]methyl]hexahydro-,
monohydrochloride,
(3aR,4S,7R,7aS)- (9CI)
OTHER NAMES:
CN Lurasidone hydrochloride
CN SM 13496
FS STEREOSEARCH
DR 441351-20-8
MF C28 H36 N4 O2 S . Cl H
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS,
EMBASE,
IMSRESEARCH, IPA, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
CRN (367514-87-2)

Absolute stereochemistry.



● HCl

SET EXPAND CONTINUOUS
L1 2 S E3-E4

FILE 'CAPLUS' ENTERED AT 12:31:30 ON 20 JUL 2010

L2 29 S L1
L3 3 S L2 AND (STARCH OR ?PRE!GELATIN? OR ACCUGEL? OR ABSORBO? OR AC
L4 3 S L3 AND (PY<=2005 OR AY<=2005 OR PRY<=2005)

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN
AB A preparation for oral administration comprises a pregelatinized starch comprising N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3- tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3- bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone hydrochloride) as an active ingredient; a water-soluble excipient; and a water-soluble polymeric binder, where the preparation exhibits an invariant level of elution behavior even when the content of its active ingredient is varied. For example, tablets were formulated containing lurasidone 80, mannitol 144, pregelatinized starch 80, croscarmellose sodium 4, hydroxypropyl Me cellulose 8, and Mg stearate 4 mg per tablet and film coated with a composition containing hydroxypropyl Me cellulose, titania, polyethylene glycol, and carnauba wax.
ACCESSION NUMBER: 2006:1252571 CAPLUS Full-text
DOCUMENT NUMBER: 146:13212
TITLE: Oral pharmaceutical compositions of lurasidone
INVENTOR(S): Fujihara, Kazuyuki
PATENT ASSIGNEE(S): Dainippon Sumitomo Pharma Co., Ltd., Japan
SOURCE: PCT Int. Appl., 42pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006126681	A1	20061130	WO 2006-JP310571	20060526 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,

AZ, BY,
KG, KZ, MD, RU, TJ, TM
AU 2006250340 A1 20061130 AU 2006-250340
20060526 <--
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EP 1884242 A1 20080206 EP 2006-746900
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PRIORITY APPLN. INFO.: JP 2005-153508 A
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IPCI A61K0031-496 [I,A]; A61K0009-20 [I,A]; A61K0047-10 [I,A];
A61K0047-26
[I,A]; A61K0047-38 [I,A]; C07D0417-12 [I,A]; C07D0417-00 [I,C*]
IPCR A61K0031-496 [I,C]; A61K0031-496 [I,A]; A61K0009-20 [I,C];
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[I,A]; A61K0047-10 [I,C]; A61K0047-10 [I,A]; A61K0047-26 [I,C];
A61K0047-26 [I,A]; A61K0047-38 [I,C]; A61K0047-38 [I,A]; C07D0417-
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[I,C]; C07D0417-12 [I,A]
CC 63-6 (Pharmaceuticals)
IT 63-42-3, Lactose 69-65-8, D-Mannitol 9005-25-8D, Starch,
pregelatinized 367514-87-2, Lurasidone 367514-88-3
, Lurasidone hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of lurasidone with improved dissoln. profile)
IT Pharmaceutical tablets
(coated tablets; oral compns. of lurasidone with improved
dissoln.
profile)
IT Dissolution
Particle size
Pharmaceutical granules
Pharmaceutical tablets
(oral compns. of lurasidone with improved dissoln. profile)
IT 63-42-3, Lactose 69-65-8, D-Mannitol 9005-25-8D, Starch,
pregelatinized 367514-87-2, Lurasidone 367514-88-3
, Lurasidone hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of lurasidone with improved dissoln. profile)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(2 CITINGS)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE
RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN
AB Disclosed are oral compns. containing a hardly water-soluble active ingredient and having favorable disintegration characteristics which comprise a molded solid article (for example, granules) obtained by mixing the hardly water-soluble active ingredient, a first disintegrating agent and a water-soluble filler with the use of a water-soluble polymer binder and then mixing this molded solid article with a second disintegrating agent, or a molded solid article obtained by mixing the hardly water-soluble active ingredient, a disintegrating agent and a sugar alc. with the use of a water-soluble polymer binder. When orally administered, these prepns. show excellent elution of the active ingredient in the digestive tract. Moreover, these prepns. can show the same elution behavior at different contents of the active ingredient and thus enable the selection of the most suitable drug for each patient, which makes these prepns. highly useful in clin. medicine. A film-coated tablet was prepared form granules containing N-[4-[4-(1,2-benzisothiazole-3-yl)-1-piperazinyl]-(2R,3R)-2,3- tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3- bicyclo[2,2,1]heptanedicarboxyimide hydrochloride 10, lactose 50, sodium croscarmellose 6 mg, and polyvinyl alc. 1.2 mg, calcium hydrogen phosphate anhydride 35, crystalline cellulose 17, and magnesium stearate 0.8 mg, and a coating material containing hydroxypropyl Me cellulose 1.95, titanium oxide 0.6, concentrate glycerin 0.45 mg, and carnauba wax q.s.
ACCESSION NUMBER: 2002:240535 CAPLUS Full-text
DOCUMENT NUMBER: 136:268164
TITLE: Oral compositions with favorable disintegration
characteristics
INVENTOR(S): Fujihara, Kazuyuki
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Company, Limited, Japan
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024166	A1	20020328	WO 2001-JP7983	20010914 <--

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CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

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LR, LS,
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PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US,
             UZ, VN, YU, ZA, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE,
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PRIORITY APPLN. INFO.:                       JP 2000-288234      A
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                                             WO 2001-JP7983      W
20010914 <--
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IPCI A61K0009-16 [ICM,7]; A61K0009-20 [ICS,7]; A61K0009-30 [ICS,7];
     A61K0031-496 [ICS,7]; A61K0045-00 [ICS,7]; A61K0047-10 [ICS,7];
     A61K0047-26 [ICS,7]; A61K0047-30 [ICS,7]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-16 [I,C*];
A61K0009-16
     [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-30 [I,C*];
     A61K0009-30 [I,A]; A61K0031-496 [I,C*]; A61K0031-496 [I,A]
CC   63-6 (Pharmaceuticals)
IT   63-42-3, Lactose   69-65-8, D-Mannitol   557-04-0, Magnesium
stearate
     7757-93-9, Calcium hydrogen phosphate   9002-89-5, Polyvinyl
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alcohol
9003-39-8, Polyvinyl pyrrolidone 9004-34-6, Crystalline cellulose,
biological studies 9004-65-3, Hydroxypropyl methyl cellulose
9005-25-8, Corn starch, biological studies 74811-65-7, Sodium croscarmellose 367514-88-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. with favorable disintegration characteristics containing
hardly water-soluble active ingredients)
IT Alditols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. with favorable disintegration characteristics containing
hardly water-soluble active ingredients)
IT Drug delivery systems
(solids, oral; oral compns. with favorable disintegration characteristics containing hardly water-soluble active ingredients)
IT Drug delivery systems
(tablets, coated; oral compns. with favorable disintegration characteristics containing hardly water-soluble active ingredients)
IT Drug delivery systems
(tablets; oral compns. with favorable disintegration characteristics
containing hardly water-soluble active ingredients)
IT Polymers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(water-soluble; oral compns. with favorable disintegration characteristics
containing hardly water-soluble active ingredients)
IT 63-42-3, Lactose 69-65-8, D-Mannitol 557-04-0, Magnesium stearate
7757-93-9, Calcium hydrogen phosphate 9002-89-5, Polyvinyl alcohol
9003-39-8, Polyvinyl pyrrolidone 9004-34-6, Crystalline cellulose,
biological studies 9004-65-3, Hydroxypropyl methyl cellulose
9005-25-8, Corn starch, biological studies 74811-65-7, Sodium croscarmellose 367514-88-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. with favorable disintegration characteristics containing
hardly water-soluble active ingredients)
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD
(8 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN
AB Disclosed are pH-independent sustained release prepns. capable of releasing a drug independently from the pH value in the gastric tract. These sustained release prepns. are characterized in that a

drug-containing core is coated with (1) a first layer made of a water-insol. polymer, and (2) a second layer made of an enteric polymer and a water-soluble polymer. Core granules were prepared containing perospirone·HCl, crystalline cellulose, PVP, starch and silica. The granules were coated with a first composition containing Et cellulose, talc, tri-Et citrate, ethanol, and water, and then a second composition containing methacrylate copolymer, PVP, sucrose ester, Macrogol 6000, and water.

ACCESSION NUMBER: 2001:762782 CAPLUS Full-text
DOCUMENT NUMBER: 135:322722
TITLE: Coating agents for sustained-release oral preparations containing basic drugs
INVENTOR(S): Nishii, Hiroyuki; Kobayashi, Hirohisa; Otoda, Kazuya
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001076557	A1	20011018	WO 2001-JP3024	20010409 <--

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PRIORITY APPLN. INFO.: JP 2000-107671 A 20000410 <--
IPCI A61K0009-14 [ICM,7]; A61K0009-16 [ICS,7]; A61K0009-36 [ICS,7]; A61K0009-30 [ICS,7,C*]; A61K0047-32 [ICS,7]; A61K0047-38 [ICS,7]; A61K0031-4178 [ICS,7]; A61K0031-4164 [ICS,7,C*]; A61K0031-496 [ICS,7]; A61K0031-506 [ICS,7]; A61K0031-5377 [ICS,7]; A61K0031-5375 [ICS,7,C*]
IPCR A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-30 [I,C*]; A61K0009-36 [I,A]; A61K0009-50 [I,C*]; A61K0009-50 [I,A]
CC 63-6 (Pharmaceuticals)

IT 9002-89-5, Polyvinyl alcohol 9003-39-8, Polyvinylpyrrolidone
9004-35-7, Cellulose acetate 9004-38-0, Cellulose acetate phthalate
9004-57-3, Ethyl cellulose 9004-64-2, Hydroxypropyl cellulose
9004-65-3, Hydroxypropyl methyl cellulose 9004-67-5, Methyl cellulose
21829-25-4, Nifedipine 25086-15-1, Methacrylic acid-methyl methacrylate
copolymer 25212-88-8, Ethyl acrylate-methacrylic acid copolymer
37205-99-5, Carboxymethyl ethyl cellulose 68377-91-3, Arotinolol
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RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymeric coating agents for sustained-release oral prepns. containing
basic drugs)
IT Drug delivery systems
(granules, sustained release; polymeric coating agents for sustained-release oral prepns. containing basic drugs)
IT Drug delivery systems
(microgranules, sustained-release; polymeric coating agents for sustained-release oral prepns. containing basic drugs)
IT Dissolution rate
(polymeric coating agents for sustained-release oral prepns. containing
basic drugs)
IT Drug delivery systems
(tablets, sustained-release; polymeric coating agents for sustained-release oral prepns. containing basic drugs)
IT 9002-89-5, Polyvinyl alcohol 9003-39-8, Polyvinylpyrrolidone
9004-35-7, Cellulose acetate 9004-38-0, Cellulose acetate phthalate
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Levofloxacin 112457-95-1, Tandospirone citrate 129273-38-7
150915-41-6, Perospirone 367514-87-2 367514-88-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymeric coating agents for sustained-release oral prepns. containing
basic drugs)

PTO/SB/30 (06-09)
Approved for use through 06/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	11/919,678
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	1627
Examiner Name	Sarah Pihonak
Attorney Docket Number	7379/98100

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 06-1135 .

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

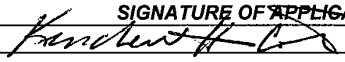
      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature		Date	January 21, 2011
Name (Print/Type)	Kendrew H. Colton	Registration No.	30,368

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SE ND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Attorney Docket No.: 7379/98100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:		
Kazuyuki FUJIHARA	Confirmation No.:	6965
U.S. Application No.: 11/919,678	Examiner:	PIHONAK, SARAH
Filed: October 31, 2007	Group Art Unit:	1627

For: PHARMACEUTICAL COMPOSITION

AMENDMENT

January 21, 2011

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Kindly enter this Amendment and grant the concurrently filed Petition for Extension of Time.

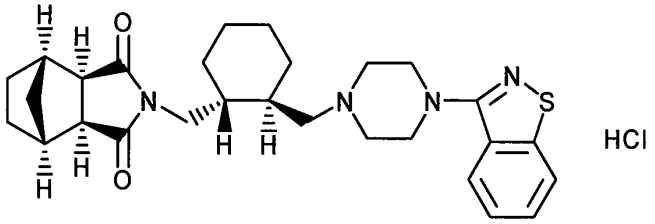
1. **Amendments to Claims** begin on page 2 of this paper.
2. **Remarks/Arguments** begin on page 8 of this paper.

Amendments to the Claims:

This listing of claims replaces any and all prior claim lists.

Listing of Claims:

1. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

2. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

3. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder;

wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

4. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose.

5. (Withdrawn) A method for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

6. (Withdrawn) A method for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by using a solution or dispersion of lurasidone and a water-soluble polymer binder.

7. (Withdrawn) The method of claim 5 wherein the water-soluble excipient is mannitol or lactose.

8. (Canceled)

9. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10. (Canceled)

11. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

12. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. (Canceled)

16. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17-18. (Canceled)

19. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

20. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Previously Presented) The oral preparation of claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Previously Presented) The oral preparation of claim 1 wherein an average particle size of lurasidone is 0.1 to 8 μm.

23. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

25. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 20 to 45% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

26. (Previously Presented) The oral preparation of claim 9 wherein the water-soluble excipient is mannitol or lactose.

27. (New) The oral preparation of claim 1 wherein a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt).

28. (New) The oral preparation of claim 1 wherein the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose.

29. (New) The oral preparation of claim 1 wherein a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

30. (New) The oral preparation of claim 1, further comprising a disintegrant wherein a content of the disintegrant per tablet is 0.5 to 5% (wt/wt).

31. (New) The oral preparation of claim 1, further comprising a disintegrant wherein
a content of the disintegrant per tablet is 0.5 to 5% (wt/wt);
the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation;
a content of lurasidone per tablet is 40 to 120 mg;
a pregelatinizing ratio of the pregelatinized starch is 50 to 95%;
an average particle size of lurasidone is 0.1 to 8 μm;
the pregelatinized starch contains water soluble matter of 30% or less;
a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt);
the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose; and

a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

32. (New) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 160 mg.

33. (New) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 80 to 160 mg.

34. (New) The oral preparation of either one of claim 1 or 31, wherein a similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg.

35. (New) A method for treating psychosis, comprising administering the oral preparation of claim 1 to a patient suffering from psychosis.

36. (New) A method for treating schizophrenia, comprising administering the oral preparation of claim 1 to a patient suffering from schizophrenia.

REMARKS

Applicants courteously solicit favorable reconsideration followed by a Notice of Allowance.

Upon entry of this Amendment claims 1-7, 9, 11-14, 16, 19-36 will be presented. New claims 27-36 find basis in the original specification. Paragraph [0017] supports new claim 27. Paragraph [0018] supports new claims 28 and 29. Paragraph [0020] supports new claim 30. New claim 31 reflects a combination of various claims, such as claims 1, 9, 14, 21-23, and 27-30. Paragraph [0015] supports new claim 32. Results of Tests 2-5 provide support for new claim 33. New claim 34 is supported by the similar dissolution profile shown in Tests 9 and 13, Figure 3 and the similarity factor f2 can be calculated by paragraphs [0029] and[0030]. Paragraph [0015] supports new claims 35 and 36. The new claims avoid new matter and entry thereof is courteously solicited.

Applicants acknowledge the previous Office Action at page 2 and respectfully solicit allowance of the group I claims, and rejoinder of the withdrawn method claims 5-7 is also requested. Applicants notes the rejoinder offered in the previous Office Action, page 2, paragraph 2.

Traversal of Rejection under 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 1-4 and 8-24 under 35 U.S.C. §103(a) over Fujihara *et al.* (EP Patent Publication No. 1327440) in view of Salpekar *et al.* (U.S. Patent No. 4,600,579).

By way of background, aspects of the present claimed inventions involve an oral preparation that may comprise high contents of a hardly-soluble pharmaceutically active agent (e.g. lurasidone), yet the preparation exhibits a similar dissolution profile as compared to oral preparations having different contents of such pharmaceutically active agent (*see* paragraph [0013]). An aspect of the present invention includes an oral

preparation having pregelatinized starch in the amount of 10-50% wt/wt per oral preparation.

The claims would not have been obvious over Fujihara *et al.*
in view of Salpekar *et al.*
- <u>Fujihara does not teach the higher wt/wt amounts of lurasidone.</u>

Although Fujihara discloses an oral composition comprising lurasidone which provides dissolution characteristics, Fujihara's 16.3% (wt/wt) or less of lurasidone is definitely different from the currently claimed invention in the content rates of lurasidone per oral preparation. This difference is one of the distinguishing aspects of the present claimed of the invention.

Fujihara only discloses that tablets comprising 8.13-16.3% (wt/wt) of lurasidone may have advantageous dissolution characteristics, and does not teach that any tablets comprising more than 16.3% (wt/wt) of lurasidone show remarkable dissolution profiles. In this respect, Fujihara's tablets of Comparative Examples 1-3, including a tablet comprising 29% of lurasidone (Comparative Example 3), are significantly inferior to the corresponding FC tablets of Examples 2-28 which comprise 8.13-16.3% (wt/wt) of lurasidone in terms of the dissolution characteristics (see [0185], [0191] and [0197]). Fujihara thus teaches away. Accordingly, Fujihara neither discloses nor suggests the claim 1 oral preparation comprising high amounts (20-45% (wt/wt)) of lurasidone which shows excellent dissolution profiles.

Furthermore, Fujihara's method does not yield (allow) compositions having high contents of lurasidone to show excellent dissolution profiles. As clearly disclosed in Test 1 (Tables 1-5, Figure 2 and Comparative Examples 1 and 2) of the original description, two tablets of Comparative Example 1 and 2 were prepared according to Fujihara's method and comprised lurasidone in the weight of 12.3% and 24.7%, respectively. Test 1 shows that Fujihara's tablet comprising 24.7% of lurasidone (80 mg tablet) clearly

shows lower dissolution profile than that comprising 12.3% of lurasidone in 15 minutes (see Figure 2, Table 4, [0039]). In contrast, the present oral preparation has favorable dissolution rates and similar dissolution profiles between tablets (see Test 1, Figure 3, Tables 1-3, 13). As shown in Figure 3, dissolution rates of three tablets are more than 80% in 15 minutes. Table 4 and Figure 3 show that these tablets have similar dissolution profiles.

Whereas Fujihara does not disclose compositions comprising more than 16.3% (wt/wt) of lurasidone which show advantageous dissolution profiles as it only discloses those comprising 16.3% (wt/wt) or less of lurasidone, the instant invention provides a composition comprising 20% (wt/wt) or more of lurasidone which shows a remarkably advantageous dissolution profile. The advantageous dissolution profiles for the high content rates of lurasidone may result from inclusion of the recited amount of pregelatinized starch, which is not taught or suggested by Fujihara.

- Fujihara's shortcomings are not overcome, even if, for the sake of argument it were combined with Salpekar *et al.*

Although Salpekar *et al.* teaches a composition comprised of a pharmaceutically active ingredient and pregelatinized starch, and even if *arguendo* some of such compositions with other additives and amounts may allow a shorter dissolution time and may shorten the dissolution and disintegration time, as the Examiner apparently postulates, Salpekar *et al.* nonetheless does not provide any motivation towards the claimed inventions.

- No expectation of Applicant's success and an element of teaching away.

There is a teaching away element to Salpekar *et al.* and a lack of an expectation of the success achieved in utilizing the pregelatinized starch within the range of recited in the claims.

Salpekar *et al.*'s Examples 1-3 are relevant, and suggest Salpekar *et al* apparently does not teach what is asserted in the Office Action. The disintegration time of the Example 1 tablet (18.0% pregelatinized starch, "PGS") is 18.0 minutes, which is 2 to 12 (200% to 1200%) times longer than the Example 2 tablet (6 minutes) and the Example 3 tablet (1.5 minutes). Salpekar *et al.* explains at column 8, lines 44-49 that "As indicated in these examples, Example 1 contains neither auxiliary binder nor auxiliary disintegrating agent; Example 2 includes an auxiliary binder but no auxiliary disintegrating agent; and Example 3 includes both an auxiliary binder and an auxiliary disintegrating agent."

Salpekar et al.'s Examples and related disclosures show that too large amounts of PGS, such as the 18.0% in Example 1, do not improve the disintegration time as well as the dissolution profile of the tablet.

Sepekar et al. teaches, however, that only a combination of small amounts of pregelatinzed starch ("PGS"), such as 8.85 % or 6.4%, and at least an auxiliary binder disclosed can improve disintegration time.

On the other hand, claim 1 recites "the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation," which is far from Sepekar *et al.*'s disclosed value of 8.85%.

Sepekar et al. uses a much more water soluble active ingredient than lurasidone. The former would not predict results obtained with the latter.

Specifically, the pharmaceutically active ingredient used by Salpekar *et al.* is N-acetyl-p-aminophenol (Acetaminophen) (see lines 6-14 of column 1). According to DrugBank (http://www.drugbank.ca/drugs/DB00316), the experimental water solubility of acetaminophen is 14 mg/mL (see the attachment). In contrast, the water solubility of lurasidone is 0.224 mg/mL at 20°C which is extremely lower (approximately 1/62.5) than that of acetaminophen.

That means that lurasidone is much more difficult from the solubility standpoint than acetaminophen, and that Salpekar *et al.* just relates to a comparatively soluble agent "acetaminophen," not to a hardly-soluble agent.

Therefore, the improvement in disintegration time in Salpekar *et al.* must be caused by the good water solubility for acetaminophen. It would have been ***un***reasonable to expect Salpekar *et al.*'s disclosure regarding good water soluble agents to be appropriate for the hardly soluble lurasidone.

Salpekar *et al.* discloses that a preferred embodiment is a composition comprising 93-83% of acetaminophen (see line 63, column 5 to line 9, column 6). Those skilled in the art cannot apply Salpekar's formulation for comparatively soluble agents including extremely high contents (93-83%) of the active ingredient to tablets comprising a hardly-soluble lurasidone in order to solve the problem of the undesired dissolution profiles of hardly-soluble agents in any conventional compositions. The higher contents of the different material in Salpekar teach away from the claim 1 oral preparation.

Even if, for the sake of argument, Salpekar *et al.* were combined with Fujihara, a person skilled in the art cannot arrive at the pregelatinized starch (10 to 50% (wt/wt)) in the claims. Although Salpekar *et al.* teaches that effective amount of PGS (i.e., pregelatinized starch) is from about 5 or less to about 15 or more parts per 100 parts of the composition (see lines 15-17 of column 4), Salpekar's compositions which substantially show significant technical effects are only those supported by Examples (i.e., 4.45-8.85% of PGS), in view of Salpekar's disclosure that the PGS is included in an amount effective for imparting to the composition the capability of being formed into tablets having high hardness, short disintegration time (e.g., about 10 minutes or less) and short dissolution time (e.g., about 20 minutes or less for 80% or more of the APAP to dissolve) (see lines 3-9 of column 4).

As discussed previously, from Table of column 8 and taking lines 3-9 of column 4 into consideration, the Example 1 tablet (18.0% of PGS) is not acceptable in order to

solve Salpekar's problem, since the disintegration time of Example 1 tablet is 18.0 minutes which is 3-12 (300% to 1200%) times longer than that of Example 2 (6 minutes) or Example 3 tablet (1.5 minutes). Even the Example 2 tablet comprising 8.85% of PGS is not perfectly acceptable in terms of it having a 4 (400%) times longer disintegration time than Example 3 tablet.

Therefore, those skilled in the art may understand that 4.45-8.85% of PGS is preferable for a tablet having a short disintegration time and a short dissolution time. Accordingly, a person of ordinary skill in the art cannot arrive at pregelatinized starch (10 to 50% (wt/wt)), beyond Salpekar's preferable ranges, which can cause compositions comprising high content rates of the active ingredient with the advantageous dissolution profiles.

Conclusion

Applicant has found that it is possible to provide an oral preparation which includes a high concentration of lurasidone (20 to 45 wt./wt.%) in combination with 10 to 50 wt./wt.% pregelatinized starch that provides advantageous dissolution profiles. None of the prior art documents, alone or in combination, would have taught or suggested this combination of features or that the advantages can be achieved therewith.

In view of the above amendment and remarks, Applicant respectfully request favorable reconsideration of the instant application in the form of a Notice of Allowance.

The Examiner is encouraged to telephone the undersigned with any comments, suggestions or questions concerning the application for further constructively advancing patent prosecution.

Applicants hereby request that any concurrent or future reply submitted by Applicants to the U.S. Patent and Trademark Office in connection with the above-identified patent application requiring an extension of time under 37 C.F.R. §1.136(a) for its timely submission be treated as incorporating therein a request for an extension of time for the appropriate length of time. In addition, to the extent necessary during prosecution of the present application, Applicants hereby authorize the Commissioner to charge any required fee not otherwise provided for, including application processing, extension, and extra claims fees, to Deposit Account No. 06-1135 with reference to Attorney Docket No. **7379/98100**.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

/Kendrew H. Colton/

Kendrew H. Colton
Registration No. 30,368

Please send official correspondence to:
Customer Number 42798

FITCH, EVEN, TABIN & FLANNERY
1120 20th St., NW, Suite 750 South
Washington, DC 20036
Tel: (202) 419-7000
Fax: (202) 419-7007

PTO/SB/22 (06-09)
Approved for use through 06/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** ***(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)***	Docket Number (Optional) 7379/98100
Application Number 11/919,678	Filed October 31, 2007
For PHARAMACEUTICAL COMPOSITION	
Art Unit 1627	Examiner Sarah Pihonak

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$130	$65	$
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☑ Three months (37 CFR 1.17(a)(3))	$1110	$555	$ 1110.00
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 06-1135.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

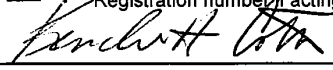
I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 30,368

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____



Signature — January 21, 2011 — Date

Kendrew H. Colton — Typed or printed name

(202) 419-7000 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal

Application Number:	11919678
Filing Date:	31-Oct-2007
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Filer:	Kendrew H. Colton/Lois Ford
Attorney Docket Number:	7379/98100

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**1920**

Electronic Acknowledgement Receipt	
EFS ID:	9279145
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	42798
Filer:	Kendrew H. Colton/Lois Ford
Filer Authorized By:	Kendrew H. Colton
Attorney Docket Number:	7379/98100
Receipt Date:	21-JAN-2011
Filing Date:	31-OCT-2007
Time Stamp:	13:34:26
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1920
RAM confirmation Number	10625
Deposit Account	061135
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees) Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	**Document Description**	**File Name**	**File Size(Bytes)/ Message Digest**	**Multi Part /.zip**	**Pages (if appl.)**
1	Request for Continued Examination (RCE)	RCE-January21.pdf	70608 0b3424efbb9a304eb12df2e2508819bbcf2bc068	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2		Amendment-January21.pdf	513405 2a37247b58059b7ba2a55e59f918c93f511eea2a	yes	14
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
	Claims		2	7	
	Applicant Arguments/Remarks Made in an Amendment		8	14	
Warnings:					
Information:					
3	Extension of Time	Petition-EOT.pdf	59903 935c8302943485d0edcc97e12c26093710db103e	no	1
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	31897 7e6101b790087c1271c7dd61f32937683da1165d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	675813		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/919,678	10/31/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/21/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 24	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***5	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TIFFIANY n. TABB/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11919678
	Filing Date	2007-10-31
	First Named Inventor	Kazuyuki Fujihara
	Art Unit	1627
	Examiner Name	Sara Pihonak
	Attorney Docket Number	7379/98100

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11919678
	Filing Date	2007-10-31
	First Named Inventor	Kazuyuki Fujihara
	Art Unit	1627
	Examiner Name	Sara Pihonak
	Attorney Docket Number	7379/98100

	1	EPO Communication dated Feb. 1, 2012, with enclosed Supplemental Search Report, in EPO Appln. 11181100.6	☐
	2	Kibbe, Handbook of Pharmaceutical Excipients, Chapter 7, pages 528-530 (2000)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11919678
	Filing Date	2007-10-31
	First Named Inventor	Kazuyuki Fujihara
	Art Unit	1627
	Examiner Name	Sara Pihonak
	Attorney Docket Number	7379/98100

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Kendrew H. Colton/	Date (YYYY-MM-DD)	2012-03-07
Name/Print	Kendrew H. Colton	Registration Number	30368

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Electronic Acknowledgement Receipt

EFS ID:	12241196
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	42798
Filer:	Kendrew H. Colton
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Attorney Docket Number:	7379/98100
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Filing Date:	31-OCT-2007
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Application Type:	U.S. National Stage under 35 USC 371

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	D3.pdf	160553 c21ed8321d4fc247b0a16fae0ff38cea79dc12c0	no	3
Warnings:					
Information:					

2	Non Patent Literature	EESR.pdf	419625 bc62e2fd262baef9192d2fa8eb5b17a81859ef8c	no	10
Warnings:					
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3	Information Disclosure Statement (IDS) Form (SB08)	updated_IDS7March2012.pdf	611842 765fd8f661c71d28956340d5c5eebc96234676d9	no	4
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	7379/98100	6965

42798 7590 03/13/2012

FITCH, EVEN, TABIN & FLANNERY, LLP
P. O. BOX 18415
WASHINGTON, DC 20036

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
03/13/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/919,678	FUJIHARA, KAZUYUKI	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-7,9,11-14,16 and 19-36* is/are pending in the application.

5a) Of the above claim(s) *5-7,35 and 36* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-4,9,11-14,16 and 19-34* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/7/2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application, filed 10/31/2007, is a national stage entry of PCT/JP2006/310571, filed on 5/26/2006.

Priority

This application claims foreign priority to Application No. 2005-153508, filed on 5/26/2005.

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/21/2011 has been entered.

Response to Remarks

2. Claims 1-7, 9, 11-14, 16, 19-36 are pending as of the amendments filed on 1/21/2011. Claims 5-7 were previously withdrawn from consideration, due to the restriction requirement.

3. Newly submitted claims 35-36 are directed to an invention that is independent or distinct from the invention originally elected for examination for the following reasons: claims 35-36 are directed to a method of treating psychosis and schizophrenia, while the elected claims of 1-4, 9, 11-14, and 19-34 are directed to an oral preparation comprised of lurasidone HCl, pregelatinized starch, and a water soluble excipient. The inventions are related as a product and a process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the elected invention of a product comprised of an oral preparation comprised of lurasidone, pregelatinized starch, and a water soluble excipient can be used for purposes other than the methods as cited in claims 35 and 36, such as in toxicology testing assays.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 35-36 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicant's arguments over the rejection under 35 USC 103(a) as being unpatentable over Fujihara, EP 1327440, in view of Salpekar et. al., US Patent No. 4,600,579, have been fully considered but are not found persuasive. The Applicant has argued that the claimed oral composition comprised of lurasidone

HCl, a pregelatinized starch, and a water-soluble excipient would not have been prima facie obvious to one of ordinary skill in the art, because Fujihara discloses that only tablets comprised of 8.13 to 16.3% of lurasidone have advantageous dissolution profiles, and that the tablet comprised of 29% lurasidone has a significantly inferior dissolution profile. The Applicant asserts that one of ordinary skill in the art would not have looked to Fujihara to have prepared an oral composition comprised of 20 to 45% by weight lurasidone. The examiner respectfully disagrees, because while the Applicant asserts that Fujihara only discloses beneficial dissolution profiles for tablets having 16.3% or less of lurasidone, the examiner maintains that Fujihara explicitly teaches that oral compositions comprised of up to 40 mg. lurasidone have good disintegration, and equivalent dissolution profiles to tablets comprised of lower amounts of lurasidone (see Fujihara, p. 2, paragraphs [0001] and [0004-0005]; p. 5, paragraph [0015]). A reference is interpreted for the teachings as a whole, and not only for working examples and preferred embodiments. See MPEP 2123; *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.). Furthermore, Applicant's direct comparison of the claimed composition to the composition taught by Fujihara is not found to be persuasive, as the rejection was based upon the combination of Fujihara and Salpekar et. al., and it was acknowledged in the office action dated 7/27/2010 that Fujihara does not explicitly teach the incorporation of a pregelatinized starch. Salpekar et. al. teaches the benefits of incorporating a pregelatinized starch into an oral composition, such as imparting improved disintegration and dissolution profiles.

Fujihara teaches lurasidone HCl as only slightly water soluble, thus one of ordinary skill in the art would have been motivated to have incorporated a pregelatinized starch into the composition, with the expectation of improving the dissolution and thus bioavailability of lurasidone HCl.

The Applicant has argued that Salpekar et. al. does not provide any motivation towards the claimed invention and teaches away from the claimed composition. The Applicant cites examples 1-3 from Salpekar as teaching away from the claimed composition, asserting that the examples and disclosure of Salpekar show that too large amounts of pregelatinized starch do not improve the disintegration time or dissolution profile of the tablet. The Applicant has argued that Salpekar et. al. teaches only the combination of a small amount of pregelatinized starch, such as 8.85% and 6.4%, along with an auxiliary binder improve the disintegration time. The examiner respectfully disagrees, because as discussed above, a reference is to be relied upon for all of its teachings, and not only exemplifications or preferred embodiments. The examiner maintains that Salpekar et. al. teaches a pregelatinized starch, such as Starch 1500, for decreasing disintegration and dissolution times for tablets (see column 3, lines 46-51; column 4, lines 31-37). Salpekar et. al. also explicitly teaches an effective amount of pregelatinized starch to range from about 5 or less to about 15 parts of more per 100 parts of the composition (column 4, lines 15-17); thus, one of ordinary skill in the art would not have limited the amount of pregelatinized starch in the oral tablet to comprise 8.85% and 6.4%, or less than these amounts. The Applicant has argued that the active agent present in the composition taught by

Salpekar et. al. is acetaminophen, which is much more water soluble than lurasidone HCl. The Applicant asserts that due to the differences in water solubility between the active agents, one of ordinary skill in the art could not have reasonably utilized the teachings of Salpekar et. al. to predict the claimed composition. The Applicant has also pointed out that the composition taught by Salpekar employs a high percentage of acetaminophen, which teaches away from the claimed composition. The examiner respectfully disagrees, as Salpekar et. al. explicitly teaches the incorporation of a pregelatinized starch for improving dissolution and disintegration times. Additionally, Salpekar's teachings are not limited to tablets comprised of high amounts of acetominophen (see Abstract). While the examiner has considered Applicant's argument that the water solubilities of acetaminophen and lurasidone HCl differ, the examiner maintains that one of ordinary skill in the art, in consideration of Salpekar's teachings of improving dissolution times by incorporation of a pregelatinized starch, would have been motivated to have incorporated a pregelatinized starch into an oral composition comprised of an active agent with low water solubility, for the purpose of improving the dissolution of the active drug. The rejection under 35 USC 103(a) as being unpatentable over Fujihara, in view of Salpekar et. al., was proper and is maintained, for reasons of record. A modified rejection under 103(a) over Fujihara in view of Salpekar et. al. has been made, in consideration of the new claims, which will be discussed in the office action. A new rejection for obviousness type double patenting has been made, which will be discussed in the office action.

4. Claims 1-4, 9, 11-14, 16, and 19-34 were examined.

5. Claims 1-4, 9, 11-14, 16, and 19-34 are rejected.

Claim Rejections-35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-4, 9, 11-14, 16, and 19-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujihara et. al., EP Patent Publication No. 1327440, in view of Salpekar et. al., US Patent No. 4,600,579 (both of previous record).

The claims are drawn to an oral composition comprised of lurasidone, pregelatinized starch, a water soluble excipient such as mannitol or lactose, and

a water soluble polymer binder. The claims are also drawn to the composition in which the pregelatinized starch is present in an amount from 10-50% by weight, and in which the lurasidone is present in an amount from 25 to 45% by weight.

Fujihara et. al. teaches an oral composition comprised of a slightly water soluble active ingredient, such as lurasidone, along with a first disintegrant, a second disintegrant, and a water soluble polymer binder (Abstract; p. 4-5, paragraph [0008]). Fujihara et. al. teaches that the composition provides advantageous dissolution characteristics when ingested (Abstract). Corn starch is taught and exemplified as a first disintegrant (p. 4, lines 6-9; p. 5, paragraph [0011]; p. 22, paragraph [0152], Ex. 28). It is taught that one of the water soluble excipients includes sugar alcohols such as mannitol or lactose (p. 3, paragraph [0017], item (18); p. 5, paragraph [0014]). The other disintegrant is taught as including excipients such as microcrystalline cellulose, croscarmellose sodium, among others (p. 5, paragraph [0011]), and the water soluble polymer binder includes polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl methylcellulose, and others (p. 4, lines 10-12; p. 5, paragraph [0010]). It is taught that the amount of lurasidone present in the oral composition is 40 mg., which is within the range instantly claimed (p. 5, paragraph [0015]; p. 22, paragraph [0152], Table 28), and that the average particle size of lurasidone is between 0.5 to 5 μm (p. 6, paragraph [0021]). It is taught that for a tablet of a weight of approximately 142 mg., the amount of lurasidone present is 40 mg., which is approximately 28 % of the weight of the composition (p. 29, paragraph [0194], Table 44). The water soluble polymer binder is taught to comprise from about 1 to 10% by weight of

the preparation (p. 4, lines 39-40), and water soluble excipients such as mannitol or lactose are taught to comprise from 200 to 2000 % by weight to the weight of lurasidone (p. 9, paragraph [0066]), however, Fujihara et. al. provides an example wherein mannitol is present in an amount of 94 mg., and lurasidone present in an amount of 20 mg. (p. 20, Table 24, paragraph [0145]), in addition to another example wherein lurasidone comprises 40 mg. of the tablet, while mannitol comprises 132 mg., of a total mass of 250 mg. for the tablet (p. 23, paragraph [0159], Table 32, Ex. 24). Thus, Fujihara teaches a water soluble excipient such as D-mannitol or lactose to comprise about 53% of the tablet (p. 23, paragraph [0159], Ex. 24 of Table 32; 132 mg./250 mg. is about 53%), which is within the amount range of water soluble excipient cited in the claimed composition. Fujihara provides an example formulation wherein the amount of the disintegrant crosscarmellose sodium is 4.8 % of the tablet weight (12 mg. for a 250 mg. tablet; p. 23, paragraph [0159], Table 32); therefore, the limitation of claim 30 is met. It is taught that the oral preparation comprises a granule, which is prepared by granulating the water-soluble polymer binder with the powdery mixture consisting of the active agent (lurasidone), a water soluble excipient, and another disintegrant (p. 3, paragraph [0007], items (11-13); p. 4, paragraph [0007], item (40)). Fujihara et. al. teaches that the preparation can be formulated as pills, granules, fine granules, capsules, tablets, etc. (p. 5, paragraph [0016]).

Fujihara et. al. does not explicitly teach that the composition comprises pregelatinized starch, in an amount from 10 to 50% by weight of the composition. It is not explicitly taught that the composition comprises 80 mg. of lurasidone.

Salpekar et. al. teaches that a composition comprised of a pharmaceutically active ingredient, a lubricant, a disintegrant, and pregelatinized starch allows for high hardness, and short dissolution time when ingested (Abstract). Salpekar et. al. teaches that the composition comprised of the pregelatinized starch is beneficial for preparing oral pharmaceutical formulations such as tablets (column 1, lines 22-29). It is taught that the partially pregelatinized starch, such as the starch commercially known as Starch 1500, acts as a binder to the composition, and provides beneficial disintegrant properties, as well as increasing hardness of the composition and shortening the dissolution and disintegration time (column 3, lines 38-51; column 4, lines 31-37). Salpekar et. al. teaches that the amount of partially pregelatinized starch ranges from 5 or less to 15 or more parts per 100 parts of the composition (column 4, lines 15-17), which is within the amount of pregelatinized starch instantly claimed. It is taught that the amount of pregelatinized starch present is based upon the amount necessary to impart the high hardness and decreased dissolution times to the composition (column 4, lines 3-9); therefore, it would have been obvious to one of ordinary skill in the art that the optimum range of the pregelatinized starch may comprise amounts greater than or less than 5-15 % by weight, as taught. Salpekar et. al. teaches that the percent gelatinization of the pregelatinized starch ranges optimally from 50 to 75% (column 2, lines 33-55). Additionally, it is taught that Starch 1500 has a moisture content between 3 and 5 % (column 3, lines 38-45).

One of ordinary skill in the art would have been motivated, at the time of the invention, to have prepared the oral lurasidone preparation taught by Fujihara et. al. with incorporation of the pregelatinized starch excipient taught by Salpekar et. al. because Salpekar et. al. teaches that the pregelatinized starch in oral pharmaceutical formulations provides beneficial properties, such as increased hardness of the tablet, decreased dissolution time after ingestion, and short disintegration time. As such, it would have been prima facie obvious for one of ordinary skill in the art to have prepared the oral lurasidone composition as taught by Fujihara et. al. with the pregelatinized starch excipient as taught by Salpekar et. al. because both Fujihara et. al. and Salpekar et. al. teach pharmaceutical compositions formulated for oral administration, and Salpekar teaches the addition of a pregelatinized starch for improving the dissolution time of the active agent. One of ordinary skill in the art would have been motivated to have incorporated pregelatinized starch, within the amount range as claimed, with a reasonable expectation that the dissolution and solubility of lurasidone HCl would have been improved. Properties associated with a composition are not patentably separable from the composition itself; see MPEP 2141.02, *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). Therefore, as it would have been prima facie obvious to have prepared an oral composition comprised of lurasidone HCl, pregelatinized starch, within the amount ranges as cited, in addition to a water-soluble excipient, it would have been prima facie obvious that properties associated with the composition, such as the similarity factor f2, which is cited as being in the range of $50 \leq f2 \leq 100$ when a content of

lurasidone per tablet changes over a range of 20 mg. to 120 mg., would also have been present. Fujihara explicitly teaches oral preparations comprised of lurasidone HCl up to 40 mg.; however, one of ordinary skill in the art would have expected success in incorporating a greater amount of lurasidone HCl in the preparation, as the pregelatinized starch taught by Salpekar et. al. improves the solubility and dissolution of the drug. It would have been obvious as such to have incorporated 80 mg. to 160 mg. of lurasidone HCl into the oral preparation, with the expectation that the presence of the pregelatinized starch, as taught by Salpekar, would have allowed for effective solubility and dissolution of the drug. Therefore, there would have been an expectation of success in utilizing the pregelatinized excipient for the composition comprising lurasidone, because it is taught by Salpekar et. al. that the pregelatinized starch imparts beneficial properties such as improvement of dissolution and disintegration to oral formulations.

Claim Rejections-Obviousness Type Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application

claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-4, 9, 11-14, 16, and 19-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 12/997779. Although the conflicting claims are not identical, they are not patentably distinct from each other because: the co-pending claims and the instant claims are directed to compositions which overlap considerably in scope. The instantly claimed composition is directed to

an oral composition comprised of lurasidone HCl in an amount between 20% to 45% by weight, a pregelatinized starch in an amount from about 10% to about 50% by weight, and a water soluble excipient; the co-pending claims are directed to a tablet comprised of an active ingredient in an amount not less than 25% by weight, mannitol, a pregelatinized starch, and a disintegrant. The claimed composition also comprises the ingredients cited in the co-pending claims, and as such the claims are not patentably separable.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Information Disclosure Statement

11. The information disclosure statement (IDS) submitted on 3/7/2012 was filed after the mailing date of the final office action on 7/27/2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Conclusion

12. No claim is currently found allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 7:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
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	34			✓						
	35			N						
	36			N						

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     FILE 'REGISTRY' ENTERED AT 12:26:29 ON 08 MAR 2012
L3            1 S 367514-87-2/RN
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     FILE 'REGISTRY' ENTERED AT 12:26:55 ON 08 MAR 2012
L4            1 S 367514-88-3/RN

L4   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2012 ACS on STN
RN   367514-88-3  REGISTRY
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     2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-
     piperazinyl]methyl]cyclohexyl]methyl]hexahydro-, hydrochloride (1:1),
     (3aR,4S,7R,7aS)-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   4,7-Methano-1H-isoindole-1,3(2H)-dione,
     2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-
     piperazinyl]methyl]cyclohexyl]methyl]hexahydro-, monohydrochloride,
     (3aR,4S,7R,7aS)- (9CI)
OTHER NAMES:
CN   Lurasidone hydrochloride
CN   SM 13496
FS   STEREOSEARCH
DR   441351-20-8
MF   C28 H36 N4 O2 S . Cl H
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS,
EMBASE,
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USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); PROC
       (Process); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  BIOL (Biological study); PREP (Preparation);
       USES (Uses)
CRN  (367514-87-2)

Absolute stereochemistry.
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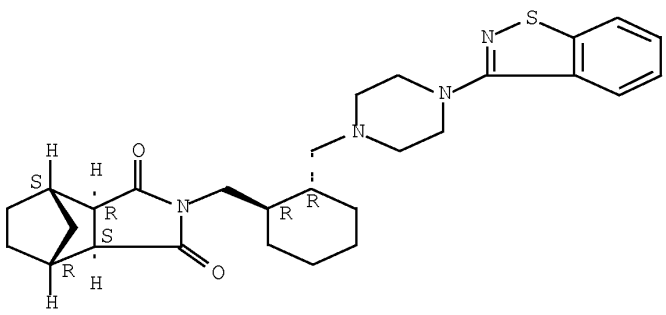

● HCl

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E E3+ALL/CT
L5 52184 S E22-E23,E29-E30,E32
E DISSOLUTION/CT
E E44+ALL/CT
L6 113293 S E55-E56,E73
E E47+ALL/CT
L7 62485 S E79-E80
L8 2 S L2 AND (L3 OR L4)

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2012 ACS on STN
AB Disclosed are oral compns. containing a hardly water-soluble active ingredient and having favorable disintegration characteristics which comprise a molded solid article (for example, granules) obtained by mixing the hardly water-soluble active ingredient, a first disintegrating agent and a water-soluble filler with the use of a water-soluble polymer binder and then mixing this molded solid article with a second disintegrating agent, or a molded solid article obtained by mixing the hardly water-soluble active ingredient, a disintegrating agent and a sugar alc. with the use of a water-soluble polymer binder. When orally administered, these prepns. show excellent elution of the active ingredient in the digestive tract. Moreover, these prepns. can show the same elution behavior at different contents of the active ingredient and thus enable the selection of the most suitable drug for each patient, which makes these prepns. highly useful in clin. medicine. A film-coated tablet was prepared form granules containing N-[4-[4-(1,2-benzisothiazole-3-yl)-1-piperazinyl]-(2R,3R)-2,3- tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3- bicyclo[2,2,1]heptanedicarboxyimide hydrochloride 10, lactose 50, sodium croscarmellose 6 mg, and polyvinyl alc. 1.2 mg, calcium hydrogen phosphate anhydride 35, crystalline cellulose 17, and magnesium stearate 0.8 mg, and a coating material containing hydroxypropyl Me cellulose 1.95, titanium oxide 0.6, concentrate glycerin 0.45 mg, and carnauba wax q.s.
ACCESSION NUMBER: 2002:240535 CAPLUS Full-text

DOCUMENT NUMBER: 136:268164
TITLE: Oral compositions with favorable disintegration characteristics
INVENTOR(S): Fujihara, Kazuyuki
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Company, Limited, Japan
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024166	A1	20020328	WO 2001-JP7983	20010914
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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EP 1327440	A1	20030716	EP 2001-965637	20010914
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EP 1974724	A3	20081112		
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ES 2325764	T3	20090916	ES 2001-965637	20010914
JP 4868695	B2	20120201	JP 2002-528202	20010914
TW 289062	B	20071101	TW 2001-123036	20010919
TW 289063	B	20071101	TW 2005-103731	20010919
US 20040028741	A1	20040212	US 2003-381036	20030321
US 7727553	B2	20100601		

PRIORITY APPLN. INFO.:	JP 2000-288234	A	20000922
	EP 2001-965637	A3	20010914
	WO 2001-JP7983	W	20010914

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IPCI A61K0009-16 [ICM,7]; A61K0009-20 [ICS,7]; A61K0009-30 [ICS,7]; A61K0031-496 [ICS,7]; A61K0045-00 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-30 [ICS,7]
IPCR A61K0009-00 [I,A]; A61K0009-16 [I,A]; A61K0009-20 [I,A]; A61K0009-30 [I,A]; A61K0031-496 [I,A]
CC 63-6 (Pharmaceuticals)
IT 63-42-3, Lactose 69-65-8, D-Mannitol 557-04-0, Magnesium stearate 7757-93-9, Calcium hydrogen phosphate 9002-89-5, Polyvinyl alcohol 9003-39-8, Polyvinyl pyrrolidone 9004-34-6, Crystalline cellulose, biological studies 9004-65-3, Hydroxypropyl methyl cellulose 9005-25-9, Corn starch, biological studies 74811-65-7, Sodium croscarmellose 367514-88-3

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. with favorable disintegration characteristics containing
hardly water-soluble active ingredients)
IT 9005-25-8, Corn starch, biological studies 367514-88-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. with favorable disintegration characteristics containing
hardly water-soluble active ingredients)

L9 6709 S L2 AND L5
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L11 1513 S L9 AND L6
L12 412 S L11 AND (PY<=2006 OR PRY<=2006 OR AY<=2006)
L13 152795 S (IMPROV? OR INCREASE?)(S)(DISSOL? OR SOLUB?)
L14 193 S L11 AND L13
L15 39 S L14 AND (PY<=2006 OR PRY<=2006 OR AY<=2006)

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FILE 'CAPLUS' ENTERED AT 14:06:04 ON 08 MAR 2012
L16 61 S L3 OR L4
L17 21 S L16 AND (AY<=2006 OR PRY<=2006 OR PY<=2006)

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11919678
	Filing Date	2007-10-31
	First Named Inventor	Kazuyuki Fujihara
	Art Unit	1627
	Examiner Name	Sara Pihonak
	Attorney Docket Number	7379/98100

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EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11919678
	Filing Date	2007-10-31
	First Named Inventor	Kazuyuki Fujihara
	Art Unit	1627
	Examiner Name	Sara Pihonak
	Attorney Docket Number	7379/98100

	1	EPO Communication dated Feb. 1, 2012, with enclosed Supplemental Search Report, in EPO Appln. 11181100.6	☐
	2	Kibbe, Handbook of Pharmaceutical Excipients, Chapter 7, pages 528-530 (2000)	☐

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EXAMINER SIGNATURE

Examiner Signature	/Sarah Pihonak/	Date Considered	03/08/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P./

EAST Search History (Prior Art)

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L3	3215	dainippon.as.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:20
L4	232	((pregelatinize$1 or pregelatinise$1) with starch).ab.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:21
L5	1	l3 and l4	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:21
L6	1	l1 and l4	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:22
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S3	2622	pre-gelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
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S5	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S6	25	S2 and S5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:55

EAST Search History (Prior Art)

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S9	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S10	446	S9 and oral	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:02
S11	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:17
S12	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S13	1	S11 and S12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
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S21	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S22	745	S21 and (starch adj "1500")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
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EAST Search History (Prior Art)

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S44	6	"2005009999".pn.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:15
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S47	41	S45 and S46	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:51

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search in EAST, PALM	11/12/2009	S.P.
Invention and claims search in EAST, STN	11/12/2009	S.P.
Inventor search in EAST, PALM	7/12/2010	S.P.
Invention and claims search in EAST, STN	7/12/2010	S.P.
invention and claims search updated in EAST, STN	3/8/2012	S.P.
updated inventor and assignee search in EAST, PALM	3/8/2012	S.P.

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/S. P./ Examiner.Art Unit 1627	

PTO/SB/22 (09-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 7379/98100
Application Number 11/919,678	Filed October 31, 2007
For PHARMACEUTICAL COMPOSITION	
Art Unit 1627	Examiner Sarah Pihonak

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$150	$75	$
☐ Two months (37 CFR 1.17(a)(2))	$560	$280	$
☑ Three months (37 CFR 1.17(a)(3))	$1270	$635	$ 1270
☐ Four months (37 CFR 1.17(a)(4))	$1980	$990	$
☐ Five months (37 CFR 1.17(a)(5))	$2690	$1345	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 06-1135.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 30,368

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Kendrew H. Colton/	13 September 2012
Signature	Date
Kendrew H. Colton	(202) 419-7000
Typed or printed name	Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal

Application Number:	11919678
Filing Date:	31-Oct-2007
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Filer:	Kendrew H. Colton/Lois Ford
Attorney Docket Number:	7379/98100

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1270	1270

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**1270**

Electronic Acknowledgement Receipt

EFS ID:	13734662
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	42798
Filer:	Kendrew H. Colton/Lois Ford
Filer Authorized By:	Kendrew H. Colton
Attorney Docket Number:	7379/98100
Receipt Date:	13-SEP-2012
Filing Date:	31-OCT-2007
Time Stamp:	14:14:41
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1270
RAM confirmation Number	424
Deposit Account	061135
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Extension of Time	PetitionEOT-13Sept2012.pdf	55352 cf83572627e78201ebde01583e963743aa2b14a7	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	29902 43b033c20da766766020707e2b46725d6d2cedaa	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	85254	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
Kazuyuki FUJIHARA	:	Confirmation No.: 6965
U.S. Application No.: 11/919,678	:	Examiner: PIHONAK, SARAH
Filed: October 31, 2007	:	Group Art Unit: 1627
	:	Attorney Docket No.: 7379/98100

For: PHARMACEUTICAL COMPOSITION

AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Kindly enter this Amendment and grant the concurrently filed Petition for Extension of Time. This Amendment should be considered together with the concurrently filed Appendix.

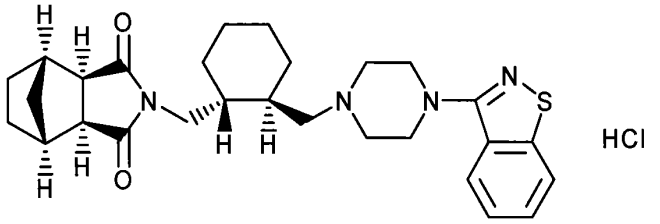
TABLE OF CONTENTS

Amendments to the Claims:

This listing of claims replaces any and all prior claim lists.

Listing of Claims:

1. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

2. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

3. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder;

wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

4. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose.

5. (Withdrawn) A method for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

6. (Withdrawn) A method for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by using a solution or dispersion of lurasidone and a water-soluble polymer binder.

7. (Withdrawn) The method of claim 5 wherein the water-soluble excipient is mannitol or lactose.

8. (Canceled)

9. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10. (Canceled)

11. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

12. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. (Canceled)

16. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17-18. (Canceled)

19. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

20. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Previously Presented) The oral preparation of claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Currently amended) The oral preparation of claim 1 wherein ~~an average~~ a 50% by volume particle size of lurasidone is 0.1 to 8 μm.

23. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

25. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 20 to 45% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

26. (Previously Presented) The oral preparation of claim 9 wherein the water-soluble excipient is mannitol or lactose.

27. (Previously submitted) The oral preparation of claim 1 wherein a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt).

28. (Previously submitted) The oral preparation of claim 1 wherein the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose.

29. (Previously submitted) The oral preparation of claim 1 wherein a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

30. (Previously submitted) The oral preparation of claim 1, further comprising a disintegrant wherein a content of the disintegrant per tablet is 0.5 to 5% (wt/wt).

31. (Currently amended) The oral preparation of claim 1, further comprising a disintegrant wherein

a content of the disintegrant per tablet is 0.5 to 5% (wt/wt);

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation;

a content of lurasidone per tablet is 40 to 120 mg;

a pregelatinizing ratio of the pregelatinized starch is 50 to 95%;

~~an average~~ 50% by volume article size of lurasidone is 0.1 to 8 μm;

the pregelatinized starch contains water soluble matter of 30% or less;

a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt);

the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose; and

a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

32. (Previously submitted) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 160 mg.

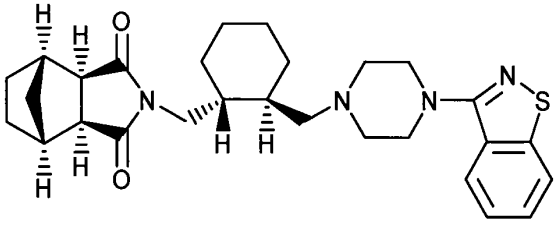
33. (Previously submitted) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 80 to 160 mg.

34. (Previously submitted) The oral preparation of either one of claim 1 or 31, wherein a similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg.

35. (Withdrawn) A method for treating psychosis, comprising administering the oral preparation of claim 1 to a patient suffering from psychosis.

36. (Withdrawn) A method for treating schizophrenia, comprising administering the oral preparation of claim 1 to a patient suffering from schizophrenia.

37. (New) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, wherein the oral preparation contains 20 to 45% (wt/wt) of lurasidone, the oral preparation contains 20 mg to 120 mg of lurasidone, the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the oral preparation, and the oral preparation exhibits an equivalent dissolution profile across the range of lurasidone per oral preparation.

REMARKS

Applicant courteously solicits favorable reconsideration upon entry of this Amendment and consideration of the concurrently filed Appendix (evidence).

Claims Presented

Upon entry of this Amendment claims 1-7, 9, 11-14, 16, and 19-37 are presented. Claims 5-7 and 35-36 are withdrawn.

Amended claims 22 and 31 are supported by the original specification, including page 8 at the bottom (see paragraph [0015]). New claim 37 find basis in the original specification, including original claim 1 and elsewhere in the original specification, such as in paragraphs [0001], [0008], [0009] and [0013], to mention examples. The new and amended claims avoid new matter and entry thereof is courteously solicited.

Rejoinder is requested.

Applicant respectfully solicits rejoinder of the withdrawn claims 5-7 and 35-36.

Claims 1-4, 9, 11-14, 16 and 19-34 define unobvious inventions over Fujihara and Salepakar.

Applicants respectfully traverse the rejection of claims 1-4, 9, 11-14, 16, and 19-34 under 35 U.S.C. §103(a) over Fujihara *et al.* (EP Patent Publication No. 1327440) in view of Salpekar *et al.* (U.S. Patent No. 4,600,579).

Aspects of the claims inventions verus the references.

Aspects of the present claimed inventions involve an oral preparation that can comprise higher contents of a hardly-soluble pharmaceutically active agent (e.g. lurasidone), yet the preparation exhibits a similar dissolution profile as compared to

oral preparations having different contents of such pharmaceutically active agent (*see, e.g.*, specification, paragraphs [0001], [0008]-[0009] and [0013]; the examples and FIG. 3.).

More particularly, characteristics of the present invention include:

1) the oral preparation of the present invention includes a high lurasidone content per tablet, particularly high content ratio (%) of 20 to 45% (wt/wt) of lurasidone as recited in claim 1[1] - which allows the employment of relatively high total amounts of lurasidone in a tablet of relatively small size – while, at the same time, the oral preparation exhibits beneficial dissolution properties (*see, e.g.*, paragraph [0106]);

2) the oral preparation of the present invention incorporates pregelatinized starch in a range of 10 to 50% (wt/wt) based on the weight of the preparation; and

3) the preparation of the present invention has beneficial dissolution properties, that is, it shows equivalent dissolution profiles as between oral preparations having different contents of lurasidone, as reflected by a similarity factor (f2) of ≥ 50[2], and furthermore exhibits rapid dissolution (*e.g.*, a dissolution of at least 85% of the initially present lurasidone within 30 minutes).

In short, an oral preparation provides a high content ratio of lurasidone (which allows employing comparatively higher amounts of lurasidone in relatively small tablets) that, at the same time, exhibiting rapid dissolution. Equivalent dissolution profiles ($f2 \geq 50$) as between the oral preparations having different lurasidone contents is an advantage. This combination of advantageous properties results from the presence of pregelatinized starch in the claimed oral preparation in an amount of 10 to 50% (wt/wt) based on the weight of the preparation, as can be seen from the data shown in the as discussed in this Amendment.

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[1] The Office Action mistakenly refers to the amounts as 25 to 45% at page 8, line 3. That amount is in dependent claims, but not independent claims 1, 2, 3 or 37.

[2] Dependent claim 34 provides an oral preparation according to claim 1 or 31 has a similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg.

As demonstrated below, Fujihara (the primary reference) does not teach or suggest an oral preparation which contains lurasidone in a content ratio of lurasidone of 20 to 45% (wt/wt)) (claims 1, 2 and 3) that can include, for instance, 20 mg to 120 mg lurasidone per oral preparation (dependent claim 13, independent claim 37), is completely silent on the use of pregelatinized starch, does not teach or disclose a pregelainized starch in an amount of 10 to 50% (wt/wt) based on the weight of the preparation (independent claims 1, 2, 3, and 37), and does not disclose or teach an oral preparation with the superior dissolution properties obtainable with a present oral preparation, such as equivalent dissolution profiles at different contents of lurasidone[3] (*see, e.g.*, claim 37), as reflected by a similarity factor (f2) of $\geq$ 50 (note dependent claim 34), and also rapid dissolution (*e.g.*, a dissolution of at least 85% of the initially present lurasidone within 30 minutes).

As also demonstrated below, these and other shortcomings of Fujihara would not have been overcome even if, for the sake of argument, Salpekar were additionally considered, which combination would not have been made in any event.

Fujihara does not motivate towards the higher % wt/wt amounts of lurasidone.

In one of its aspects, the present invention is an oral preparation which comprises lurasidone, "wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt)" as recited in claims 1, 2, and 3, for example.

Fujihara neither discloses nor suggests the claim 1 oral preparation having a content of lurasidone in the preparation of 20 to 45% (wt/wt) and that such an oral preparation exhibits excellent dissolution profiles.

Rather, as discussed below Fujihara would have focused a person of ordinary skill on an oral composition comprising lesser amounts of lurasidone which provides dissolution characteristics.

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[3] *In re Papesch*, 137 U.S.P.Q 143 (CCPA 1963).

Based on the data shown in Figure 1 attached to the original specification and the data from original Tables 26 to 28 in the original specification, data is summarized and presented for convenience in the following Table 1. The 30-minutes dissolution values are provided as a courtesy and were calculated based on the data shown in the original specification.

Table 1
Comparative formulations which do not contain pregelatinized starch based on Fujihara et al. formulations*

	A	**B**
(mg/tablet)	10 mg tablet Fig. 1, Tables 26-28	40 mg tablet Fig. 1, Tables 26-28 (Comp. Ex.1)
Lurasidone	10	40
Mannitol	47	188
Croscarmellose Na	4	16
Hydroxypropyl Methylcellulose	2.5	10
Lactose	15.5	62
Magnesium Stearate	1	4
f2	77 (A vs. B)	
Lurasidone Content Ratio (%) (in core tablet)	*12.5%*	*12.5%*
Lurasidone Content Ratio (%)(in FC tablet)	12.2%	12.3%
30-minute dissolution values	91%	92%

** Tablets in Table 1 were manufactured according to Fujihara as the Examiner will see from Test 7 in the original specification. Fujihara (as cited by the Examiner) is the same as the patent document 2 in the original specification.*

The data in Table 1 make the case that in formulations "A" and "B," the smaller content ratio of lurasidone such as 12.2% and 12.3%, falls outside of the range of 20 to 45% (wt/wt) in independent claims 1, 2, 3 and 37, as well as the "25 to 40%" in dependent claims 11, 16, 19, 24, 25, which additionally means the amount lurasidone in milligrams (mg) in formulations A and B must be distinct from the range recited in dependent claims 12-14 and 31-34 as well as independent claim 37.

Furthermore, the Fujihara preparations have a considerably smaller content ratio of lurasidone per oral preparation than the presently claimed formulations. The Fujihara preparations would make it necessary to prepare comparatively larger-sized tablets or to administer several tablets in order to treat patients in need of higher doses of lurasidone as compared to an oral preparation of the present invention. *See, e.g.,* specification at paragraph [0005].

Fujihara teaches against higher amounts of lurasidone in an oral preparation.

Fujihara discloses that tablets comprising 8.13-16.3% (wt/wt) of lurasidone may have advantageous dissolution characteristics, but does not disclose a tablet comprising more than 16.3% (wt/wt) of lurasidone showing remarkable dissolution profiles. The Fujihara preparations with the low content of luradisone per preparation may show similar dissolution profiles (f2-value of 77) and rapid dissolution (30-minute dissolution ratio values of 91% and 92%, respectively).

The same may not be said for an oral preparation of Fujihara having a higher lurasidone content.

This is clearly seen from Fujihara's tablets in Comparative Examples 1-3, including a tablet comprising 29% of lurasidone (Comparative Example 3), as they are significantly *inferior* to the corresponding FC tablets of Examples 2-28 which comprise 8.13-16.3% (wt/wt) of lurasidone in terms of the dissolution characteristics (see [0185], [0191] and [0197]). The person of ordinary skill in the art would have focused on opportunity for positive results, and thus focused on the tablets with 8.13-16.3% (wt/wt) of lurasidone as in Fujihara's Examples 2-28

This is borne out in Test 1 (Tables 1-5, Figure 2 and Comparative Examples 1 and 2) of the original description, two tablets of Comparative Example 1 and 2 were prepared according to Fujihara's method and comprised lurasidone in the weight of 12.3% and 24.7%, respectively. According to Test 1, Fujihara's tablet comprising 24.7%

of lurasidone (80 mg tablet) clearly shows *lower* dissolution profile than that comprising 12.3% of lurasidone in 15 minutes (see Figure 2, Table 4, [0039]).

The data reported support the proposition that teaches away from independent claims 1, 2, 3 and 37, as well as the claims dependent from claim 1.

***Contrary to Fujihara,* oral preparations of the present invention exhibited consistent 30 minute dissolution profiles as between for oral preparations containing different amounts of lurasidone in the claimed range.**

Based on the data disclosed in Examples 1 to 3 as well as in Table 4 in the original description, data are summarized and presented in the following Table 2 for convenience. The 30-minutes dissolution values are provided as a courtesy and were calculated based on the data shown in the original specification.

Table 2
Formulations according to the presently claimed invention which contain pregelatinized starch

	E	G	F	G
(mg/tablet)	Ex.3 Table 4	Ex.1 Table 4	Ex.2 Table 4	Ex.1 Table 4
Lurasidone	20	80	40	80
Mannitol	36	144	72	144
Pregelatinized starch	20	80	40	80
Croscarmellose Na	1	4	2	4
Hydroxypropyl Methylcellulose	2	8	4	8
Magnesium Stearate	1	4	2	4
f2	**97** (E vs. G)		**88** (F vs. G)	
Lurasidone Content Ratio (%) (in core tablet)	*25%*	*25%*	*25%*	*25%*
Lurasidone Content Ratio (%) (in FC tablet)	24.4%	24.6%	24.5%	24.6%
30-minute dissolution values	**89%**	**89%**	**91%**	**89%**

As can be seen from Table 2, the formulations of Examples 1 to 3 according to the claimed invention - with different mg contents of lurasidone and a content of lurasidone in the preparation within the range of "20 to 45% (wt/wt), show 30-minutes dissolution ratio values of 89% (Example 1/formulation "G"), 91% (Example 2/formulation "F") and 89% (Example 3/formulation "E"), respectively. The formulations of Examples 1 to 3 can thus be considered to show rapid dissolution, in accordance with the U.S. FDA reference document "Guidance for Industry" which is enclosed. The latter document explains that "*an IR [i.e, immediate-release] drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes (...).*" *See* the concurrently filed Appendix, at 1 (Guidance for Industry, paragraph bridging pages 2 and 3, entitled "C. Dissolution").

A present oral preparation has favorable dissolution rates and similar dissolution profiles between tablets (see Test 1, Figure 3, the specification at Tables 1-3, 13). As shown in Figure 3, dissolution rates of three tablets are more than 80% in 15 minutes. Table 4 and Figure 3 show that these tablets have similar dissolution profiles even at a lurasidone content greater than disclosed in Fujihara.

Whereas Fujihara does not disclose compositions comprising more than 16.3% (wt/wt) of lurasidone which show advantageous dissolution profiles as it only discloses those comprising 16.3% (wt/wt) or less of lurasidone, the instant invention provides an oral preparation having "a content of lurasidone of 20% to 45% (wt/wt)," which shows a remarkably advantageous dissolution profile even at when the lurasidone content is greater than disclosed in Fujihara.

In short, oral preparations of the present invention are superior to the known preparations according to Fujihara that contain smaller ratio content (amount) of lurasidone per preparation as illustrated by comparing the data for formulations "A" and "B" in Table 1 hereinabove with the data for the formulations "E" to "G" in Table 2 hereinabove.

Oral preparations of the present invention advantageously mean a smaller-sized oral preparation for a given lurasidone content. A smaller sized oral preparation for a given lurasidone content would be more advantageous than an oral preparation having a like lurasidone content according to Fujihara.

Oral preparations of the present invention, such as seen from formulations "E", "F" and "G", are advantageous as compared to comparative formulations "A" and "B" according to Fujihara. The present oral preparations have a greater content ratio of lurasidone and thus a higher total amount of lurasidone per tablet of a given size as compared to Fujihara.

This can be conveniently illustrated by reference to the total weights and sizes required for tablets having a lurasidone content of, *e.g.*, 80 mg/tablet, 120 mg/tablet or 160 mg/tablet, which are prepared from either a comparative formulation (i.e. formulation "B"; Comparative Example 1, having a lurasidone content ratio of 12.3%) or formulation "G" (i.e. Example 1 according to the invention, having a lurasidone content ratio of 24.6%).

Large tablets are difficult to swallow, which places increased burden on the patients and can therefore be expected to prejudice patient compliance. *See, e.g.*, specification, paragraphs [0005] and [0013]. This is germane because if tablets containing a high total amount of lurasidone are prepared on the basis of the comparative formulation B of Fujihara, the total weight of the resulting tablets would amount to 648 mg (80 mg lurasidone/tablet), 972 mg (120 mg lurasidone/tablet) and 1296 mg (160 mg lurasidone/tablet), respectively, with sizes of 12.5 mm, 14.5 mm and 16 mm in diameter as conventional round tablets. Such large sized round tablets prepared according to the comparative formulation B of Fujihara would be expected to present issues with patient compliance.

On the other hand, an oral preparation according to an aspect of the present invention can have a higher content of lurasidone per oral preparation, in a smaller-

sized oral preparation (such as a round tablet) as compared to Fujihara, whereby prospects of patient non-compliance due to oral preparation size would be reduced. This is illustrated when considering tablet sizes for larger dosages of lurasidone in a tablet prepared according to formulation G. Thus, if tablets having a lurasidone content of 80 mg/tablet, 120 mg/tablet or 160 mg/tablet are prepared using formulation "G" (*i.e.*, Example 1 according to the invention), resulting tablets would have total weights of only 325 mg (80 mg lurasidone/tablet), 487.5 mg (120 mg lurasidone/tablet) and 650 mg (160 mg lurasidone/tablet) and, in the case of conventional round tablets, diameters of 10 mm, 11.5 mm and 12.5 mm, respectively. In perspective, an oral preparation formed into a conventional round tablet having 180 mg of lurasidone would be about the same size as a round tablet having 80 mg of lurasidone prepared according to Fujihara. The former tablet advantageously would be much smaller compared to a tablet having 180 mg of lurasidone prepared according to formulation "B" (illustrating Fujihara).

From another perspective, if similarly sized round tablets are considered, with an oral preparation of the present invention the number of tablets to be administered to a patient to dose a given amount of lurasidone, especially if a high amount of lurasidone needs to be administered to a patient, can be reduced compared to the number of tablets required with a similarly sized conventional tablet with a lurasidone content according to Fujihara.

Furthermore, the relevancy of an increased content ratio of lurasidone is emphasized from as seen from the News Release at page 1, first and third paragraphs, where new recommended dosage ranges are expanded to 120 mg/day and 160 mg/day, and an approval for a new tablet having 120 mg lurasidone. *See* concurrently filed Appendix at item 3.

Present oral compositions having PGS versus an oral preparation without PGS show results supporting patentability.

The data shown in the following Table 3 are summarized from the data of Example 4 in the original description and a comparative formulation (prepared in the same manner as in Example 4 except the pregelatinized starch was used 0(zero) % and instead the amount of sodium croscarmellose was increased).

Table 3

Components	Example 4 of the original specification		Comparative formulation	
	mg	wt/wt%	mg	wt/wt%
Lurasidone	80	25	80	25
Mannitol	176	55	176	55
PGS (pregelatinized starch)	40	**12.5**	0	**0**
Ac-Di-Sol (**Croscarmellose Na**)	8	**2.5**	48	**15**
HPMC (Hypromellose, **Hydroxypropyl methylcellulose**)	12	3.75	12	3.75
Magnesium stearate	4	1.25	4	1.25
Total	320	100	320	100
30-minute dissolution values	*86%*		***70%***	

As can be seen from Table 3, the 30-minute dissolution value of the tablet according to the present invention is 86% which is significantly better than the value of 70% which is achieved by the comparative formulation which does not contain pregelatinized starch. This comparative formulation did not satisfy the explanation of an immediate-release drug product in the Guidance for Industry. *See* concurrently filed Appendix, at item 1, and the paragraph bridging pages 2 and 3, entitled "C. Dissolution."

Applicant respectfully submits the evidence shows that good dissolution can be achieved by the claimed selection of pregelatized starch compared to croscarmellose.

Fujihara does not teach or suggest the pregelatinzed starch in the claims.

Claim 1 refers to an oral preparation containing "a pregelatinized starch, ...wherein ... the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation." *See also* independent claims 2, 3 and 37.

Dependent claim 9 refers to an oral preparation wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation. *See also* dependent claims 19, 20, 24, 25, and 31.

Fujihara is completely silent on the use of pregelatinized starch or on the advantages to an oral preparation having the pregelatinized startch incorporated in an amount of 10 to 50% (wt/wt).

Accordingly, the advantageous dissolution profiles for a present oral preparation having a higher content ratio of lurasidone, with the recited amount of pregelatinized starch, is neither taught nor suggested by Fujihara.

Fujihara's shortcomings are not overcome, even if, for the sake of argument it were combined with Salpekar, which is a combination that would *not* have been made by a person of ordinary skill in the art.

Fujihara in view of Salpekar nonetheless would not have provided motivation towards the claimed inventions.

As demonstrated below, this follows since Salpekar *et al.* teaches a specific composition comprising acetaminophen as the pharmaceutically active ingredient and pregelatinized starch, which is significantly more water soluble compared to the relatively water insoluble lurasidone, and even if *arguendo* some of Salpekar's

acetaminophen-containing compositions having other additives and amounts may allow a shorter dissolution time and may shorten the dissolution and disintegration time.

Selpekar teaches away from the pregelatinized starch in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

Claim 1 recites "the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation."

Salpekar effectively teaches away from this feature in claim 1 and other claims 2, 3, and 37 as examples.

First, Sepekar teaches that only a combination of small amounts of pregelatinzed starch ("PGS"), such as 8.85 % or 6.4%, and at least an auxiliary binder disclosed can improve disintegration time in the acetaminophen tablets. Sepekar's disclosed value of 8.85% or 6.4% would not have suggested an oral composition containing lurasidone and pregelatinized starch incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

Second, Salpekar's Examples and related disclosures show that larger amounts of pregelatinized starch, such as the 18.0% in Example 1, do not improve the disintegration time and the dissolution profile of the acetaminophen-containing tablet.

The poorer results reported with 18% pregelatinized starch would have led away from claim 1. More particularly, Salpekar's Examples 1-3 are teach away from the amount of pregelatinized starch in the present claims.[4] From the Table in column 8 and taking col. 4, lines 3-9 into consideration, the Example 1 tablet (18.0% of PGS) is not acceptable in order to solve Salpekar's problem, since the disintegration time of Example 1 tablet is 18.0 minutes which is 300% times longer than that the Example 2 tablet (6 minutes) and

[4] Salpekar explains at column 8, lines 44-49 that "As indicated in these examples, Example 1 contains neither auxiliary binder nor auxiliary disintegrating agent; Example 2 includes an auxiliary binder but no auxiliary disintegrating agent; and Example 3 includes both an auxiliary binder and an auxiliary disintegrating agent."

1200% times longer than the Example 3 tablet (1.5 minutes). Even the Example 2 tablet comprising 8.85% of PGS is more disadvantageous since it shows a 400% times longer disintegration time than exhibited by a tablet according to Salpekar's Example 3.

Thus, a present oral preparation having pregelatinized starch incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation would not have been suggested by the poorer results reported for Sepekar's Example 3 (18% of PGS) (*e.g.*, an increased disintegration time for the acetaminophen containing composition). Increasing the amount of pregelatinized starch would have suggested longer, not shorter disintegration times in an acetominophen tablet, but longer disintegration times would have been contrary to Salpekar's stated objective for disintegration times (col. 4, lines 3-9).

Third, even if, for the sake of argument, Salpekar *et al.* were combined with Fujihara, a person skilled in the art would not have arrived at the pregelatinized starch (10 to 50% (wt/wt)) in the independent claims. Those skilled in the art would have understood from Salpekar that 4.45-8.85% of pregelatinized starch is preferable for an acetaminophen tablet having a short disintegration time and a short dissolution time. Although Salpekar might be said to teach an effective amount of pregelatinized starch (PGS) is from about 5 or less to about 15 or more parts per 100 parts of the acetaminophen composition (*see*, col. 4, lines 15-17), Salpekar's acetaminophen compositions that show technical effects are only those supported by Examples 2 and 3 (*i.e.*, 4.45-8.85% of pregelatinized starch). This follows from Salpekar's disclosure that the pregelatized starch is included in an amount effective for imparting to the acetaminophen composition the capability of being formed into tablets having high hardness, short disintegration time (*e.g.*, about 10 minutes or less) and short dissolution time (e.g., about 20 minutes or less). *See*, col. 4, lines 3-9. In other words, Fujihara + Salpekar, even if the combination were made, which is not conceded, a person of ordinary skill in the art would have been led away from the claimed oral preparations.

Literature reports pregelatinized starch (PGS) in amounts that would have taught away from the claimed oral preparation having 10 to 50% (wt/wt) of pregelatinized starch. The literature reports typically 10% or less of PGS as does Salpekar.

As reported in the present specification, pregelatinized starch "is often used, typically, in 10% *or less* of contents as described in Non-patent Document 1." *See, e.g.,* specification, paragraph s [0006] and [0007] (emphasis added). *See also,* concurrently filed Appendix at item 2.

This supports the point that typically (conventionally) *less* than 10% (wt/wt) pregelatinized starch would have been used, which is consistent with the results Selpaker disclosed for the acetaminophen compositions.

This conventional teaching would have led away from the present oral preparations.

Sepekar discloses acetaminophen. It is markedly much more water soluble than the comparatively water insoluble lurasidone. Sepekar's results with only acetaminophen would not have led one to expect the present results obtained with the comparatively highly water *in*soluble ingredient (lurasidone), nor led to combining it with Fujihara.

Salpekar exclusively focuses on the comparatively water soluble acetaminophen[5] would not have motivated a person of ordinary skill in the art would towards an oral preparation having 10 to 50% (wt/wt) of pregelatinized starch and the comparatively water *in*soluble lurasidone as recited in the claims.

There is no evidence cited in the Office Action to suggest relating acetaminophen with lurasidone, nor evidence suggesting Sepekar's results with the former would have

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[5] Salpekar specifically and only focuses on the requirements for an acetaminophen composition. Selpekar "relates to an N-acetyl-p-amino-phenol composition" (col. 1, lines 6-7) in which "N-acetyl-p-aminophenol [is] ... hereinafter referred to sometimes as acetaminophen..."). Selpekar, col. 1, lines 11-12.

been the candidate of choice selected in discovering an oral preparation as claimed. The compounds are different. Their properties are different.

The Examiner, however, cites passages in Salpekar at col. 3, lines 46-51 and col. 4, lines 31-37, see, e.g., Office Action, page 5, lines 6-9 from the bottom, as if these passages were generic, which they are not.

Contrary to the Office Action, the actual passages in Salpekar specifically only relate to "the composition," which must contain acetaminophen. *See, e.g.*, Selpekar, Abstract, col. 1, lines 6-29, col. 1, lines 38 and 63, col. 2, line 21, col. 5, line 48, col. 6, (Tables), and the Examples.

Since Salpekar relates only to a comparatively soluble agent "acetaminophen," not to the hardly-soluble agent (lurasidone) in the claimed oral preparations, it would have been ***un***reasonable to expect Salpekar's disclosure regarding an acetaminophen composition to be appropriate for an oral preparation having a "content of [the comparatively hardly soluble] lurasidone ... [of] 20 to 45% (wt/wt)," as claimed herein.

In other words, on the present factual record, there would have been no basis to have expected Selpekar's results with acetaminophen, which is a comparatively more water soluble agent would even have made Salpekar the candidate of choice for, let alone applicable, to a lurasidone composition as in Fujihara since lurasidone is comparatively significantly more water *in*soluble because it is 1/62.5 as soluble as acetaminophen.[6]

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[6] Acetaminophen has an experimental water solubility of 14 mg/mL (DrugBank (http://www.drugbank.ca/drugs/DB00316), see the attachment to prior Amendment).
Lurasidone, however, has a water solubility of only 0.224 mg/mL at 20°C, which more than an order of magnitude less than that for acetaminophen.

Salpekar teaches amounts of a water soluble active ingredient that would not have suggested the amounts of relatively water insoluble active ingredient (lurasidone) in the present oral compositions.

The higher contents of the different material in Salpekar teach away from the claim 1 oral preparation with an oral preparation having "a content of lurasidone in the preparation [of] 20 to 45% (wt/wt)" as in claim 1, as an example.

Salpekar discloses a preferred embodiment is a composition comprising 93-83% of acetaminophen (see line 63, column 5 to line 9, column 6). Those skilled in the art would have had no expectation or motivation to apply Salpekar's formulation for acetaminophen with extremely high contents (93-83%) of that active ingredient to tablets comprising the comparatively water *insoluble* lurasidone in order to solve the problem of the undesired dissolution profiles of lurasidone in a conventional composition.

Applicant traverses the common law obviousness type double patenting rejection. Applicant requests reconsideration and withdrawal of same.

Applicant respectfully requests the Examiner to reconsider the non-statutory rejection of claims 1-4, 9, 11-14, and 19-34 over commonly owned U.S. application 12/997779 and claims 1-8 therein. This application is the earlier filed application (series "11" application) and the common law rejection over claims in a later filed application seems misplaced, and besides, such claims might be canceled or amended, or other action taken. Withdrawal of this non-statutory rejection seems appropriate and is respectfully requested.

Conclusion

Applicant respectfully solicits reconsideration and a Notice of Allowance.

Applicant has found that it is possible to provide an oral preparation having a lurasidone content in the preparation of 20 to 45% (wt/wt.) in combination with 10 to 50% (wt/wt) pregelatinized starch that provides advantageous dissolution profiles.

None of the prior art documents applied against the claims would have taught or suggested this oral preparation or its advantages.

Fujihara does not disclose or suggest a lurasidone formulation incorporated with a comparatively large amount (10 to 50% (wt/wt) based on the preparation) of a pregelatinized starch which can exhibit excellent dissolution properties, such equivalent dissolution profiles at different contents of lurasidone (as reflected by a similar factor (f2) of ≥50) and rapid dissolution (e.g. a dissolution of at least 85% of the initially present lurasidone within 30 minutes).

Salpekar's acetomimophen compositions are not apposite to the present oral preparations or to Fujihara, do not teach or even suggest any lurasidone oral preparation, and when fairly considered teach away the incorporation of the comparatively larger amount of the pregelatinized starch into an oral preparation because of undesirable disintegration times.

Even if Fujihara were combined with Salpekar et al., which is a point not conceded, the present claimed oral preparations with their advantages would have been *un*foreseen or *un*expected by a person skilled in the art.

The Examiner is cordially invited to telephone the undersigned with any comments, suggestions or questions, or to schedule an interview.

Applicant hereby requests that any concurrent or future reply submitted by Applicants to the U.S. Patent and Trademark Office in connection with the above-identified patent application requiring an extension of time under 37 C.F.R. §1.136(a) for its timely submission be treated as incorporating therein a request for an extension of time for the appropriate length of time. In addition, to the extent necessary during prosecution of the present application, Applicant hereby authorizes the Commissioner to charge any required fee not otherwise provided for, including application processing, extension, and extra claims fees, to Deposit Account No. 06-1135 with reference to Attorney Docket No. **7379/98100**.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

/Kendrew H. Colton/

Kendrew H. Colton
Registration No. 30,368

Please send official correspondence to:
Customer Number 42798

FITCH, EVEN, TABIN & FLANNERY
1120 20th St., NW, Suite 750 South
Washington, DC 20036
Tel: (202) 419-7000
Fax: (202) 419-7007

Attorney Docket No.: 7379/98100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:		
Kazuyuki FUJIHARA	Confirmation No.:	6965
U.S. Application No.: 11/919,678	Examiner:	PIHONAK, SARAH
Filed: October 31, 2007	Group Art Unit:	1627

For: PHARMACEUTICAL COMPOSITION

APPENDIX

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Kindly enter this APPENDIX (evidence) and consider same with the Amendment filed on even date herewith.

CONTENTS

The Examiner is cordially invited to telephone the undersigned with any comments, suggestions or questions concerning the application.

Applicant hereby requests that any concurrent or future reply submitted by Applicants to the U.S. Patent and Trademark Office in connection with the above-identified patent application requiring an extension of time under 37 C.F.R. §1.136(a) for its timely submission be treated as incorporating therein a request for an extension of time for the appropriate length of time. In addition, to the extent necessary during prosecution of the present application, Applicants hereby authorize the Commissioner to charge any required fee not otherwise provided for, including application processing, extension, and extra claims fees, to Deposit Account No. 06-1135 with reference to Attorney Docket No. **7379/98100**.

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FITCH, EVEN, TABIN & FLANNERY

/Kendrew H. Colton/

Kendrew H. Colton
Registration No. 30,368

Please send official correspondence to:
Customer Number 42798

FITCH, EVEN, TABIN & FLANNERY
1120 20th St., NW, Suite 750 South
Washington, DC 20036
Tel: (202) 419-7000
Fax: (202) 419-7007

Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2000
BP

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02/03/05

Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

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U.S. Department of Health and Human Services
Food and Drug Administration
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TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY[1]

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

I. INTRODUCTION

This guidance provides recommendations for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications who wish to request a waiver of in vivo bioavailability (BA) and/or bioequivalence (BE) studies for immediate release (IR) solid oral dosage forms. These waivers are intended to apply to (1) subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR dosage forms during the IND period, and (2) in vivo BE studies of IR dosage forms in ANDAs. Regulations at 21 CFR part 320 address the requirements for bioavailability (BA) and BE data for approval of drug applications and supplemental applications. Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR 320.22. This guidance explains when biowaivers can be requested for IR solid oral dosage forms based on an approach termed the Biopharmaceutics Classification System (BCS).

II. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability.[2] According to the BCS, drug substances are classified as follows:

Class 1:	High Solubility – High Permeability
Class 2:	Low Solubility – High Permeability
Class 3:	High Solubility – Low Permeability

---

[1] This guidance has been prepared by the Biopharmaceutics Classification System Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] Amidon, G. L., H. Lennernäs, V. P. Shah, and J. R. Crison, "A Theoretical Basis For a Biopharmaceutics Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability," *Pharmaceutical Research*, 12: 413-420 (1995).

Class 4: Low Solubility – Low Permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo.[2] However, when the in vivo dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of in vivo BA or BE may not be necessary for drug products containing Class 1 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods (21 CFR 320.22(e)). The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

C. Dissolution

In this guidance, an IR drug product is considered *rapidly dissolving* when no less than 85% of the labeled amount of the drug substance dissolves within 30

minutes, using *U.S. Pharmacopeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

III. METHODOLOGY FOR CLASSIFYING A DRUG SUBSTANCE AND FOR DETERMINING THE DISSOLUTION CHARACTERISTICS OF A DRUG PRODUCT

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS:

A. Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at 37 ± 1°C in aqueous media with a pH in the range of 1-7.5. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. For example, when the pKa of a drug is in the range of 3-5, solubility should be determined at pH = pKa, pH = pKa +1, pH = pKa-1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.[3] If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported along with other stability data recommended in section III.B.3.

The solubility class should be determined by calculating the volume of an aqueous medium sufficient to dissolve the highest dose strength in the pH range of 1-7.5. A drug substance should be classified as highly soluble when the highest dose strength is soluble in ≤ 250 ml of aqueous media over the pH range of 1-7.5.

[3] See the FDA guidance for industry on *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987), posted at http://www.fda.gov/guidance/index.htm.

B. Determining Drug Substance Permeability Class

The permeability class of a drug substance can be determined in human subjects using mass balance, absolute BA, or intestinal perfusion approaches. Recommended methods not involving human subjects include in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), and/or in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells. In many cases, a single method may be sufficient (e.g., when the absolute BA is 90% or more, or when 90% or more of the administered drug is recovered in urine). When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable. Chemical structure and/or certain physicochemical attributes of a drug substance (e.g., partition coefficient in suitable systems) can provide useful information about its permeability characteristics. Sponsors may wish to consider use of such information to further support a classification.

1. Pharmacokinetic Studies in Humans

a. Mass Balance Studies

Pharmacokinetic mass balance studies using unlabeled, stable isotopes or a radiolabeled drug substance can be used to document the extent of absorption of a drug. Depending on the variability of the studies, a sufficient number of subjects should be enrolled to provide a reliable estimate of extent of absorption. Because this method can provide highly variable estimates of drug absorption for many drugs, other methods described below may be preferable.

b. Absolute Bioavailability Studies

Oral BA determination using intravenous administration as a reference can be used. Depending on the variability of the studies, a sufficient number of subjects should be enrolled in a study to provide a reliable estimate of the extent of absorption. When the absolute BA of a drug is shown to be 90% or more, additional data to document drug stability in the gastrointestinal fluid is not necessary.

2. Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract: (1) in vivo intestinal perfusion studies in humans; (2) in vivo or in situ intestinal perfusion studies using suitable animal models; (3) in vitro permeation studies using excised human or animal intestinal tissues; or (4) in vitro permeation studies across a monolayer of cultured epithelial cells.

In vivo or in situ animal models and in vitro methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane transporters such as P-glycoprotein (P-gp). When the efflux transporters are absent in these models, or their degree of expression is low compared to that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared to a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) of a drug is demonstrated in humans

- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) in the perfusion fluid

- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp)

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals and for in vitro cell culture methods, twenty model drugs are recommended. Depending on study variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation between drug substances of low and high intestinal permeability attributes.

For demonstration of suitability of a method, model drugs should represent a range of low (e.g., < 50%), moderate (e.g., 50 - 89%), and high (≥ 90%) absorption. Sponsors may select compounds from the list of drugs and/or chemicals provided in Attachment A or they may choose to select other drugs for which there is information available on mechanism of absorption and reliable estimates of the extent of drug absorption in humans.

After demonstrating suitability of a method and maintaining the same study protocol, it is not necessary to retest all selected model drugs for subsequent studies intended to classify a drug substance. Instead, a low and a high permeability model drug should be used as internal standards (i.e., included in the perfusion fluid or donor fluid along with the test drug substance). These two internal standards are in addition to the fluid volume marker (or a zero permeability compound such as PEG 4000) that is included in certain types of perfusion techniques (e.g., closed loop techniques). The choice of internal standards should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions). When it is not feasible to follow this protocol, the permeability of internal standards should be determined in the same subjects, animals, tissues, or monolayers, following evaluation of the test drug substance. The permeability values of the two internal standards should not differ significantly between different tests, including those conducted to demonstrate suitability of the method. At the end of an in situ or in vitro test, the amount of drug in the membrane should be determined.

For a given test method with set conditions, selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary may facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the gastrointestinal fluid prior to intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human and/or animal gastrointestinal tract either in vivo or in situ. Documenting the fact that drug loss from the gastrointestinal tract arises from intestinal membrane permeation, rather than a degradation process, will help establish permeability. Stability in the gastrointestinal tract may be documented using gastric and intestinal fluids obtained from human subjects. Drug solutions in these fluids should be incubated at 37°C for a period that is representative of in vivo drug contact with these fluids; for example, 1 hour in gastric fluid and 3 hours in intestinal fluid. Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (>5%) of a drug in this protocol could suggest potential instability. Obtaining gastrointestinal fluids from human subjects requires intubation and may be difficult in some cases. Use of gastrointestinal fluids from suitable animal models and/or simulated fluids such as Gastric and Intestinal Fluids USP can be substituted when properly justified.

C. Determining Drug Product Dissolution Characteristics and Dissolution Profile Similarity[4]

Dissolution testing should be carried out in USP Apparatus I at 100 rpm or Apparatus II at 50 rpm using 900 ml of the following dissolution media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. For capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

Dissolution testing apparatus used in this evaluation should conform to the requirements in USP (<711> Dissolution). Selection of the dissolution testing apparatus (USP Apparatus I or II) during drug development should be based on a comparison of in vitro dissolution and in vivo pharmacokinetic data available for the product. The USP Apparatus I (*basket method*) is generally preferred for capsules and products that tend to float, and USP Apparatus II (*paddle method*) is generally preferred for tablets. For some tablet dosage forms, in vitro (but not in vivo) dissolution may be slow due to the manner in which the disintegrated product settles at the bottom of a dissolution vessel. In such situations, USP Apparatus I may be preferred over Apparatus II. If the testing conditions need to be modified to better reflect rapid in vivo dissolution (e.g., use of a different rotating speed), such modifications can be justified by comparing in vitro

[4] See the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

dissolution with in vivo absorption data (e.g., a relative BA study using a simple aqueous solution as the reference product).
A minimum of 12 dosage units of a drug product should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product (e.g., 10, 15, 20, and 30 minutes).

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f_2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

$$f_2 = 50 \bullet \log \{[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100\}$$

Two dissolution profiles are considered similar when the f_2 value is ≥ 50. To allow the use of mean data, the coefficient of variation should not be more than 20% at the earlier time points (e.g., 10 minutes), and should not be more than 10% at other time points. Note that when both test and reference products dissolve 85% or more of the label amount of the drug in ≤ 15 minutes using all three dissolution media recommended above, the profile comparison with an f_2 test is unnecessary.

IV. ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors can affect their request or the documentation of their request:

A. Excipients

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA of the drug may be requested by the Agency. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic, and sponsors are encouraged to contact the review division when this is a factor.

B. Prodrugs

Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrug and drug can be relevant. Sponsors may wish to consult with appropriate review staff before applying the BCS approach to IR products containing prodrugs.

C. Exceptions

BCS-based biowaivers are not applicable for the following:

1. Narrow Therapeutic Range Drugs[5]

This guidance defines narrow therapeutic range drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

2. Products Designed to be Absorbed in the Oral Cavity

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets).

V. REGULATORY APPLICATIONS OF THE BCS

A. INDs/NDAs

Evidence demonstrating in vivo BA or information to permit FDA to waive this evidence must be included in NDAs (21 CFR 320.21(a)). A specific objective is to establish in vivo performance of the dosage form used in the clinical studies that provided primary evidence of efficacy and safety. The sponsor may wish to determine the relative BA of an IR solid oral dosage form by comparison with an

[5] This guidance uses the term *narrow therapeutic range* instead of *narrow therapeutic index*, although the latter is more commonly used.

oral solution, suspension, or intravenous injection (21 CFR 320.25 (d)(2) and 320.25 (d)(3)). The BA of the clinical trial dosage form should be optimized during the IND period.

Once the in vivo BA of a formulation is established during the IND period, waivers of subsequent in vivo BE studies, following major changes in components, composition, and/or method of manufacture (e.g., similar to SUPAC-IR Level 3 changes[6]) may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles (see sections II and III). This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and postchange are *pharmaceutical equivalents* (under the definition at 21 CFR 320.1 (c)). BCS-based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or other pharmacokinetic studies.

B. ANDAs

BCS-based biowaivers can be requested for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances, provided that the reference listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product (see sections II and III). This approach is useful when the test and reference dosage forms are pharmaceutical equivalents. The choice of dissolution apparatus (USP Apparatus I or II) should be the same as that established for the reference listed drug product.

C. Postapproval Changes

BCS-based biowaivers can be requested for significant postapproval changes (e.g., Level 3 changes in components and composition) to a rapidly dissolving IR product containing a highly soluble, highly permeable drug substance, provided that dissolution remains rapid for the postchange product and both pre- and postchange products exhibit similar dissolution profiles (see sections II and III). This approach is useful only when the drug products pre- and postchange are pharmaceutical equivalents.

VI. DATA TO SUPPORT A REQUEST FOR BIOWAIVERS

The drug substance for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting biowaivers based on the BCS should submit the following information to the Agency for review by the Office of Clinical Pharmacology

[6] See the FDA guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes* (November 1995).

and Biopharmaceutics (for NDAs) or Office of Generic Drugs, Division of Bioequivalence (for ANDAs):

A. Data Supporting High Solubility

Data supporting high solubility of the test drug substance should be developed (see section III.A). The following information should be included in the application:

- A description of test methods, including information on analytical method and composition of the buffer solutions
- Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric, or neutral), and dissociation constants (pKa(s))
- Test results (mean, standard deviation, and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/ml), and volume of media required to dissolve the highest dose strength
- A graphic representation of mean pH-solubility profile

B. Data Supporting High Permeability

Data supporting high permeability of the test drug substance should be developed (see section III.B). The following information should be included in the application:

- For human pharmacokinetic studies, information on study design and methods used along with the pharmacokinetic data
- For direct permeability methods, information supporting the suitability of a selected method that encompasses a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations in the donor fluid, description of the analytical method, method used to calculate extent of absorption or permeability, and where appropriate, information on efflux potential (e.g., bidirectional transport data)
- A list of selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of a method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean ± standard deviation or 95% confidence interval) with identification of the low/high permeability

class boundary and selected internal standard. Information to support high permeability of a test drug substance should include permeability data on the test drug substance, the internal standards (mean, standard deviation, coefficient of variation), stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

C. Data Supporting Rapid and Similar Dissolution

For submission of a biowaiver request, an IR product should be rapidly dissolving. Data supporting rapid dissolution attributes of the test and reference products should be developed (see section III.C). The following information should be included in the application:

- A brief description of the IR products used for dissolution testing, including information on batch or lot number, expiry date, dimensions, strength, and weight

- Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods in section III.C. The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.

- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the f_2 metric

D. Additional Information

The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation vs. direct compression). A list of excipients used, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms.

ATTACHMENT A

This attachment includes model drugs suggested for use in establishing suitability of a permeability method as described in section III. The permeability of these compounds was determined based on data available to the FDA. Potential *internal standards* (IS) and *efflux pump substrates* (ES) are also identified.

Drug	Permeability Class
Antipyrine	High (Potential IS candidate)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (Potential IS candidate)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High (Potential ES candidate)
Amoxicillin	Low
Atenolol	Low
Furosemide	Low
Hydrochlorthiazide	Low
Mannitol	Low (Potential IS candidate)
α-Methyldopa	Low
Polyethylene glycol (400)	Low
Polyethylene glycol (1000)	Low
Polyethylene glycol (4000)	Low (Zero permeability marker)
Ranitidine	Low

Handbook of Pharmaceutical Excipients, 2nd edition, 491, 1994

Pregelatinized Starch

1. Nonproprietary Names

BP: Pregelatinised maize starch
USPNF: Pregelatinized starch

2. Synonyms

Compressible starch; *Instastarch*; *Lycatab PGS*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *Starch 1500*; *Sta-Rx 1500*.

3. Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4. Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$
Where n = 300-1000.
Pregelatinized starch is a starch that has been chemically and mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin and 80% unmodified starch. The USPNF XVII does not specify the botanical origin of the original starch but the BP 1993 specifies that corn (maize) starch should be used. *See also* Starch and Section 13.

5. Structural Formula

See Starch.

6. Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent[1] and disintegrant.[2]
In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry compression processes.[3-11] In such processes, pregelatinized starch is self-lubricating. However, when used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.[12]
Pregelatinized starch may also be used in wet granulation processes.[13]

Use	Concentration (%)
Diluent (hard gelatin capsules)	5-75
Tablet binder (direct compression)	5-20
Tablet binder (wet granulation)	5-10
Tablet disintegrant	5-10

8. Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.
Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules. Examination of samples suspended in glycerin show characteristic forms depending upon the method of drying used during manufacture, e.g. either irregular chunks from drum drying or thin plates.

9. Pharmacopeial Specifications

Test	BP 1993	USPNF XVII (Suppl 5)
Identification	+	+
pH (10% w/v slurry)	4.5-7.0	4.5-7.0
Iron	—	≤ 0.002%
Oxidizing substances	—	+
Sulfur dioxide	—	≤ 0.008%
Microbial limits	+	+
Loss on drying	≤ 15.0%	≤ 14.0%
Residue on ignition	—	≤ 0.5%
Sulfated ash	≤ 0.5%	—
Protein	≤ 0.5%	—

10. Typical Properties

Acidity/alkalinity: pH = 4.5-7.0 for a 10% w/v aqueous dispersion.
Angle of repose: 40.7°[6]
Flowability: 18-23% (Carr compressibility index)[14]
Moisture content: pregelatinized maize starch is hygroscopic,[11,15,16] *see* HPE Data.
Particle size distribution: 30-150 μm, median diameter 52 μm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 μm), and less than 0.5% retained on a US #40 mesh (420 μm).
Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Fully pregelatinized starch conforms to the completeness of solution test in the USP XXII. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold water soluble matter for partially pregelatinized starch is 10-20%.
Specific surface area: 0.21-0.22 m^2/g
Viscosity (dynamic): 8-10 mPa s (8-10 cP) for a 2% w/v aqueous dispersion at 25°C.

	HPE Laboratory Project Data Method	Lab #	Results*
Bulk/tap density			
Starch 1500	BTD-7	14	B: 0.650 g/cm^3 [a] T: 0.820 g/cm^3
Moisture content	MC-22	2	7.0% [b]
	MC-15	34	8.94% [b]
	EMC-1	2	*See* Fig. 1. [b]
Starch 1500	MC-15	34	11.12% [a]
Starch 1500	MC-15	14	11.30% [a]
Starch 1500	SDI-1	14	*See* Fig. 2. [a]
Wheat (*Paygel 90*)	MC-15	14	6.60% [c]
Wheat (*Paygel 90*)	SDI-1	14	*See* Fig. 2. [c]
Particle size	PSD-2	5	68 μm [b]
Starch 1500	PSD-2	5	80 μm [a]

Supplier: a. Colorcon Ltd; b. National Starch & Chemicals Ltd; c. Henkel Corp.
* Note that results are for pregelatinized corn starch unless otherwise indicated.

11. Stability and Storage Conditions

Pregelatinized starch is a stable, though hygroscopic material, which should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

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13. Method of Manufacture

Fully pregelatinized starch is prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62-72°C. Chemical additives which may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded or drum-dried. In the latter case, the dried material may be processed to produce a desired particle size range.
Partially pregelatinized starch is prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where partial gelatinization and subsequent drying takes place.

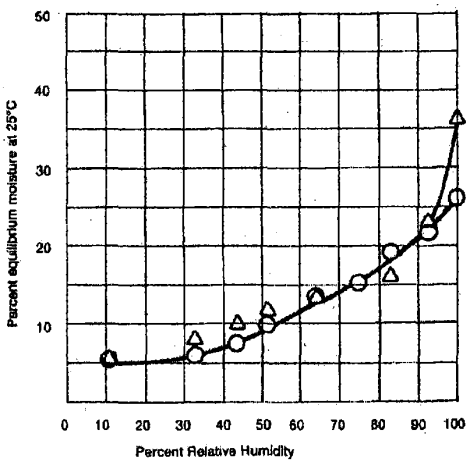

Fig. 1: Equilibrium moisture content of corn starch and pregelatinized starch.
○ Corn starch (National Starch & Chemicals Ltd; Lot #421).
△ Pregelatinized corn starch (National Starch & Chemicals Ltd; Lot #HJW 103).

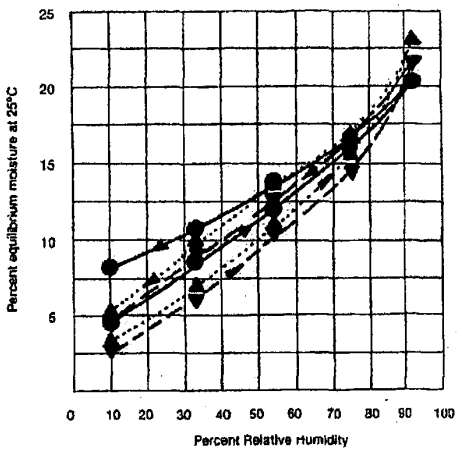

Fig. 2: Sorption-desorption isotherms of pregelatinized corn starch and pregelatinized wheat starch.
● Pregelatinized corn starch, *Sta-Rx 1500* (AE Staley Mfg Co; Lot #977912).
▲ Pregelatinized wheat starch, *Paygel 90* (Henkel Corp; Lot #289D).
▼Pregelatinized corn starch, *Starch 1500* (Colorcon Ltd; Lot #904014)

14. Safety

Pregelatinized starch, and starch, are widely used in oral solid dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of pregelatinized starch may be harmful.
See Starch for further information.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust-mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.
In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are, 10 mg/m^3 for total inhalable dust and 5 mg/m^3 for respirable dust.[17]

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br and USPNF.

18. Related Substances

Starch; Sterilizable Maize Starch.

19. Comments

A low moisture grade of pregelatinized starch, *Starch 1500 LM*. (Colorcon Ltd), containing less than 7% of water, is commercially available specifically intended for use as a diluent in capsule formulations.

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22. Authors

USA: NG Lordi.

Sunovion Pharmaceuticals Inc.
84 Waterford Drive, Marlborough, MA 01752-7010
Tel 508-481-6700

News Release

Contact: Susan Alesina
Vice President, Corporate Communications
Sunovion Pharmaceuticals Inc.
508-481-6700
susan.alesina@sunovion.com

Latuda® (lurasidone HCl) Label Updated With Expanded Dosing Range Providing Added Flexibility for the Treatment of Patients with Schizophrenia

Marlborough, Mass., May 5, 2012 – Sunovion Pharmaceuticals Inc. today announced that the U.S. Food and Drug Administration (FDA) has approved an expanded dose range for LATUDA in the treatment of adult patients with schizophrenia. The FDA decision followed a review of the supplemental New Drug Application (sNDA), which was submitted in June 2011.

The maximum recommended dose of LATUDA was increased from 80 mg/day to 160 mg/day based in part on data from a 6-week placebo and active-controlled trial (N=482) involving two fixed doses of LATUDA (80 mg/day or 160 mg/day) and an active control (quetiapine XR 600 mg/day). In this study[1], both LATUDA doses demonstrated statistically significant improvement at the Week 6 study endpoint compared to placebo in change from baseline in Positive and Negative Syndrome Scale total score (PANSS, primary efficacy endpoint) and the Clinical Global Impression-Severity scale (CGI-S, key secondary efficacy endpoint). The active control (quetiapine XR) also separated from placebo on the PANSS total and CGI-S scale at study endpoint. The LATUDA safety profile in this study was consistent with prior studies in patients with schizophrenia; no new safety concerns were identified.

The newly expanded recommended dose range for LATUDA (40-160 mg/day) includes approval of the 120 mg/day and 160 mg/day doses, as well as a new 120 mg tablet. This dose range reflects positive results from five short-term studies that evaluated the safety and efficacy of LATUDA where doses of 40 mg/day, 80 mg/day, 120 mg/day and 160 mg/day were shown to be safe and effective.

"Schizophrenia is a complex disorder that requires a careful assessment of each patient. Having added dosing flexibility for LATUDA will allow physicians to better tailor treatment to the individual needs of patients with schizophrenia," said Antony Loebel, M.D., Executive Vice President and Chief Medical Officer of Sunovion Pharmaceuticals Inc.

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[1] PEARL 3 (**P**rogram to **E**valuate the **A**ntipsychotic **R**esponse to **L**urasidone) was a six-week, double-blind, placebo-controlled study to evaluate the efficacy of LATUDA in adult patients with schizophrenia. The double-blind extension study followed a core six-week, double-blind, placebo-controlled study (PEARL 3) where patients were randomized to treatment with one of the following: LATUDA 80 mg/day, LATUDA 160 mg/day, quetiapine XR 600 mg/day or placebo.

The sNDA summarized safety information derived from a clinical study database consisting of 2,905 patients with schizophrenia who were exposed to at least one dose of LATUDA. Of these patients, 1,508 participated in short-term, placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg, 120 mg or 160 mg once daily. The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and parkinsonism. There were no dose-related adverse reactions observed in patients treated with LATUDA across the 20 mg to 160 mg/day dose range compared to placebo. The frequency of akathisia increased with the dosage strength up to 120 mg/day (5.6% for LATUDA 20 mg/day, 10.7% for LATUDA 40 mg/day, 12.3% for LATUDA 80 mg/day, 22.0% for LATUDA 120 mg/day, 7.4% for LATUDA 160 mg/day and 3.0% for patients receiving placebo).

LATUDA initially received FDA approval for the treatment of schizophrenia on October 28, 2010 and is available in pharmacies across the United States and Puerto Rico.

About LATUDA
LATUDA is an atypical antipsychotic indicated for the treatment of patients with schizophrenia. Efficacy was established in five 6-week controlled studies of adult patients with schizophrenia. The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

The recommended starting dose for LATUDA is 40 mg once daily taken with food (at least 350 calories) with no initial dose titration required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 160 mg/day. The maximum recommended dose is 160 mg/day. For patients with moderate and severe renal or hepatic impairment, the recommended starting dose of LATUDA is 20 mg/day. The maximum recommended dose is 80 mg/day in patients with moderate hepatic impairment and 40 mg/day in patients with severe hepatic impairment. The recommended starting dose of LATUDA in patients taking a moderate CYP3A4 inhibitor such as diltiazem is 20 mg/day with a maximum recommended dose of 80 mg/day. LATUDA should not be administered with strong CYP3A4 inhibitors such as ketoconazole or strong CYP3A4 inducers such as rifampin.

Please see Important Safety Information, including **Boxed Warning** below, and full Prescribing Information at www.LATUDA.com.

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **LATUDA is not approved for the treatment of patients with dementia-related psychosis.**

CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole)
- Concomitant use with strong CYP3A4 inducers (e.g., rifampin).

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. In short-term, placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was -0.2 ng/mL and was 0.5 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations > 5x ULN was 1.6% versus 0.6% for placebo-treated male patients.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension and in patients with known cardiovascular disease or cerebrovascular disease.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer's dementia).

Potential for Cognitive and Motor Impairment: In short-term, placebo-controlled trials, somnolence was reported in 17.0% (256/1508) of patients treated with LATUDA compared to 7.1% (50/708) of placebo patients, respectively. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.
Suicide: The possibility of suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS
Commonly Observed Adverse Reactions: (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and parkinsonism.

Before prescribing LATUDA, please read the full Prescribing Information, including **Boxed Warning** at www.LATUDA.com.

About Schizophrenia
Schizophrenia is a chronic, disabling and serious brain disorder that affects approximately 2.4 million American adults or 1 in 100 people. Schizophrenia is characterized by symptoms such as hallucinations, delusions, disorganized thinking, lack of emotion, lack of energy, as well as problems with memory, attention and the ability to plan, organize and make decisions.

About Sunovion Pharmaceuticals Inc. (Sunovion)
Sunovion is a leading pharmaceutical company dedicated to discovering, developing and commercializing therapeutic products that advance the science of medicine in the central nervous system (CNS) and respiratory disease areas and improve the lives of patients and their families. Sunovion's drug development program, together with its corporate development and licensing efforts, has yielded a portfolio of pharmaceutical products including LATUDA® (lurasidone HCl) tablets, LUNESTA® (eszopiclone) tablets, XOPENEX® (levalbuterol HCl) inhalation solution, XOPENEX HFA® (levalbuterol tartrate) inhalation aerosol, BROVANA® (aformoterol tartrate) inhalation solution, OMNARIS® (ciclesonide) nasal spray and ALVESCO® (ciclesonide) HFA inhalation aerosol.

Sunovion, an indirect, wholly-owned subsidiary of Dainippon Sumitomo Pharma Co., Ltd., is headquartered in Marlborough, Mass. More information about Sunovion Pharmaceuticals Inc. is available at www.sunovion.com.

About Dainippon Sumitomo Pharma Co., Ltd. (DSP)
DSP is a multi-billion dollar, top-ten listed pharmaceutical company in Japan with a diverse portfolio of pharmaceutical, animal health and food and specialty products. DSP aims to produce innovative pharmaceutical products in the CNS field, which has been designated as the key therapeutic area and will also focus in on other specialty disease categories with significant unmet medical needs, which are designated as frontier therapeutic areas. DSP is based on the merger in 2005 between Dainippon Pharmaceutical Co., Ltd. and Sumitomo Pharmaceuticals Co., Ltd. Today, DSP has more than 7,000 employees worldwide. Additional information about DSP is available through its corporate website at www.ds-pharma.com.

For a copy of this release visit Sunovion's web site at www.sunovion.com

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Electronic Acknowledgement Receipt

EFS ID:	13739305
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	42798
Filer:	Kendrew H. Colton/Lois Ford
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment-13Sept2012.pdf	1070515 490760be45e5c4be5e9c2dbb6379ce3cd9366692	yes	26

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	8
	Applicant Arguments/Remarks Made in an Amendment	9	26

Warnings:					
Information:					
2	Appendix to the Specification	Appendix-13Sept2012.pdf	1252587 b6b414c9d44f7d6bc538d9c53ad1867d9dc5f279	no	26
Warnings:					
Information:					
		Total Files Size (in bytes):	2323102		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/919,678	Filing Date 10/31/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	**310**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	**310**

APPLICATION AS AMENDED – PART II

AMENDMENT	**01/21/2012**	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 31	Minus	** 24	= 7	X $ =		OR	X $60=	420
	Independent (37 CFR 1.16(h))	* 3	Minus	***5	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**420**

AMENDMENT	**09/13/2012**	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 32	Minus	** 31	= 1	X $ =		OR	X $60 =	60
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 5	= 0	X $ =		OR	X $250 =	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**60**

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/FELICIA ALLEN-JENKINS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	7379/98100	6965

42798 7590 12/11/2012

FITCH, EVEN, TABIN & FLANNERY, LLP
P. O. BOX 18415
WASHINGTON, DC 20036

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
12/11/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/919,678	FUJIHARA, KAZUYUKI	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-7,9,11-14,16 and 19-37* is/are pending in the application.

5a) Of the above claim(s) *5-7,35 and 36* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-4,9,11-14,16,19-34 and 37* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

This application, filed 10/31/2007, is a national stage entry of PCT/JP2006/310571, filed on 5/26/2006.

Priority

This application claims foreign priority to Application No. 2005-153508, filed on 5/26/2005.

Response to Remarks

1. Claims 1-7, 9, 11-14, 16, and 19-37 are pending as of the reply and amendments filed on 9/13/2012. Claims 5-7 and 35-36 were previously withdrawn from consideration, due to the restriction requirement.

Claims 1-4, 9, 11-14, 16, and 19-34 were previously rejected under 35 USC 103(a) as being unpatentable over Fujihara et. al., in view of Salpekar et. al. The Applicant has traversed this rejection with the argument that the claimed oral preparation would not have been prima facie obvious to one of ordinary skill in the art in consideration of the prior art, because Fujihara et. al. does not teach or suggest an oral preparation which contains a content ratio of lurasidone from 20 to 45 wt%, is silent to the use of pregelatinized starch, and does not teach the rapid dissolution properties of the instantly claimed oral preparation. The Applicant has submitted that the oral preparation taught by Fujihara et. al. has a considerably smaller content ratio of lurasidone per oral preparation than the

instantly claimed composition. The Applicant has argued that Fujihara et. al. provides a formulation tablet comprised of 29% lurasidone which is significantly inferior with regards to dissolution in comparison to tablets comprising from 8.13-16.3% of lurasidone, and thus one of ordinary skill in the art would have focused on lurasidone tablets comprised of 8.13-16.3% of lurasidone, rather than 20-45% by weight lurasidone, as instantly claimed. The Applicant has compared formulations of lurasidone tablets comprising 12.3% and 24.7% lurasidone, respectively, according to the Fujihara et. al. method, with the 24.7% lurasidone tablet having a lower dissolution profile in comparison to the 12.3% lurasidone tablet. The Applicant has further maintained that contrary to the teachings of Fujihara et. al., the claimed oral preparations containing different amounts of lurasidone within the claimed range exhibited consistent 30 minute dissolution profiles, as shown in Table 2. The Applicant has submitted that the claimed oral preparations comprised of a greater ratio content of lurasidone than that shown by Fujihara et. al. are superior to the oral preparations taught by Fujihara et. al.

The examiner has fully considered Applicant's arguments and the comparison data provided in the discussion tables as well as the appendix, but does not find them fully persuasive to overcome the rejection for obviousness over Fujihara et. al., in view of Salpekar et. al. While the Applicant has argued that the oral preparations taught by Fujihara et. al. have a poorer dissolution profile in comparison to the instantly claimed oral preparation, the examiner notes that the preparation taught by Fujihara et. al. does not comprise pregelatinized starch, which the Applicant has pointed out is important to provide

the desired dissolution profile. The Applicant has argued that the composition comprised of 29% by weight lurasidone as taught by Fujihara et. al. has a slower dissolution profile in comparison to tablets comprised of 8.13-16.3% of lurasidone, and therefore one of ordinary skill in the art would not have been motivated to have formulated an oral lurasidone preparation comprising greater than 8.13-16.3% lurasidone. The examiner does not find this argument persuasive, because Fujihara et. al. explicitly teaches a tablet comprised of 40 mg. lurasidone, or 28% of the total weight of the formulation. One of ordinary skill in the art would therefore have had a reasonable expectation of success in preparing a tablet comprised of 40 mg., or 28% by weight of the composition. Additionally, the rejection under 35 USC 103(a) was made over a combination of references, and not only the Fujihara et. al. reference. Salpekar et. al. teaches pregelatinized starch for increasing the hardness of an oral composition and shortening the dissolution and disintegration time. While the Applicant has argued that the Fujihara et. al. preparation comprised of 29% by weight lurasidone has slower dissolution time in comparison to the tablets comprised of 8.13-16.3% lurasidone, one of ordinary skill in the art would have found it prima facie obvious to have incorporated pregelatinized starch into the tablet formulation taught by Fujihara et. al. for the purpose of improving the dissolution and disintegration time. Salpekar et. al. teaches that the amount of partially pregelatinized starch ranges from 5 or less to 15 or more parts per 100 parts of the composition. The examiner maintains that one of ordinary skill in the art would have been motivated to have incorporated pregelatinized starch in an

amount taught by Salpekar et. al., which includes the cited range of pregelatinized starch in the instantly claimed preparation, with a reasonable expectation that the dissolution time of the tablet would have been shortened.

The Applicant has further argued that the instantly claimed oral preparation, exemplified in formulations “E”, “F”, and “G”, have better dissolution properties in comparison to formulations “A” and “B” as taught by Fujihara et. al. The Applicant has argued that the tablets prepared according to Fujihara et. al. would be required to be larger than the instantly claimed oral preparations, which would introduce issues with patient compliance, as the new recommended dosages of lurasidone have been expanded to 120 mg/day and 160 mg/day, as shown in Appendix at item 3. The Applicant has compared the dissolution profile of an oral preparation comprised of 80 mg. lurasidone and 12.5% pregelatinized starch with an oral preparation comprised of 80 mg. lurasidone which does not comprise pregelatinized starch but rather contains a greater amount of sodium croscarmellose to make up the difference in weight. The Applicant has submitted that as the 30 minute dissolution profile of the lurasidone + pregelatinized starch formulation is clearly greater than the formulation which does not comprise pregelatinized starch, the instantly claimed composition is allowable.

The examiner has fully considered the comparison dissolution profiles presented by the Applicant along with the discussion points, but notes that the comparisons of formulations “E”, “F”, and “G” with the Fujihara et. al. formulations “A” and “B” are not equivalent, as the instantly claimed formulations comprise pregelatinized starch, which the Applicant has submitted is important to the

improved dissolution profiles, while the formulations taught by Fujihara et. al. do not comprise pregelatinized starch. Similarly, while the Applicant has shown that the preparation comprised of 80 mg. lurasidone and 12.5% pregelatinized starch has an improved 30 minute dissolution profile in comparison to the formulation without the pregelatinized starch, the examiner maintains that this result would not have been unexpected, as Salpekar et. al. teaches the incorporation of pregelatinized starch into an oral preparation for improving the disintegration and dissolution profiles. One of ordinary skill in the art, in consideration of the combined teachings of Fujihara et. al. and Salpekar et. al., would have reasonably expected that the addition of pregelatinized starch within the amount cited in the instantly claimed preparation would have improved the dissolution time of the lurasidone oral preparation.

The Applicant has argued that Salpekar et. al. would not have rendered the claimed oral preparation prima facie obvious and in fact teaches away from the claimed invention, as Salpekar teaches a specific oral preparation comprised of acetaminophen which is significantly more water soluble in comparison to lurasidone, and additionally teaches only a combination of small amounts of pregelatinized starch and at least an auxiliary binder to improve disintegration time. The Applicant has further submitted that Salpekar et. al. teaches an example formulation comprised of 18% pregelatinized starch which does not have an improved dissolution and disintegration time over the formulations have less pregelatinized starch. It has also been argued by the Applicant that in consideration of the poorer dissolution time of the 18% pregelatinized starch oral

preparation taught by Salpekar et. al., and the preferable dissolution times of the 4.45-8.85% pregelatinized starch compositions taught by Salpekar, one of ordinary skill in the art would have been motivated to have incorporated less than 18% pregelatinized starch into an oral preparation. The Applicant has also argued several additional points, namely that Salpekar's teaching of PGS from about 5 to about 15 parts or more per 100 parts of the composition applies only to the acetaminophen composition; and that Salpekar discloses a preferred embodiment wherein the composition comprises 83-93% acetaminophen, which one of ordinary skill in the art would not have been motivated to have applied to a lurasidone preparation.

The examiner has fully considered Applicant's arguments, but they are not found fully persuasive. While the Applicant has argued that Salpekar et. al. teaches a particular composition comprised of acetaminophen, which the Applicants have submitted is considerably more water soluble than lurasidone, the examiner submits that the lurasidone preparation and preparation taught by Salpekar et. al. are both oral formulations. Salpekar et. al. teaches incorporation of pregelatinized starch in an amount of about 5 parts or less up to 15 parts or more per 100 parts of the oral composition for imparting high hardness, short disintegration, and short dissolution times. The lurasidone composition taught by Fujihara et. al. is also for oral administration. Therefore, as Salpekar et. al. teaches pregelatinized starch as an adjuvant for improving the disintegration and dissolution times of an oral preparation, one of ordinary skill in the art would have been motivated to have incorporated pregelatinized starch into another oral

preparation, such as the lurasidone preparation taught by Fujihara et. al., for the purpose of improving the disintegration and dissolution times. While the Applicant has argued that lurasidone is considerably less water soluble than acetaminophen, the examiner maintains that one of ordinary skill in the art nonetheless would have been motivated to have added pregelatinized starch within the amount range taught by Salpekar et. al. to an oral lurasidone preparation, particularly if the active agent is known to be poorly water soluble and therefore have slower dissolution, for the purpose of improving the dissolution profile. While the Applicant has argued that Salpekar et. al. implies that oral preparations comprised of 4.45-8.85% pregelatinized starch have better dissolution times in comparison to the composition comprised of 18% pregelatinized starch and thus one of ordinary skill in the art would not have been motivated to have added pregelatinized starch within the amount range cited in the instant claims, the examiner notes that the disintegration profile comparison of the examples referred to by Salpekar et. al. shows the difference in the compositions with and without an auxiliary binder and auxiliary disintegration agent. The instantly claimed oral preparation does not exclude auxiliary binders or disintegrants; thus, Salpekar's teaching of these excipients along with pregelatinized starch would not have rendered the claimed preparation unobvious. Furthermore, a prior art reference is not limited to only specific examples and preferred embodiments; see MPEP 2123. Particularly, the MPEP 2123 states that, “A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including

nonpreferred embodiments"; see *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Salpekar et. al. teaches an oral preparation which is comprised of pregelatinized starch in an amount of about 5 parts or less to 15 parts or more, per 100 parts of the composition, for improving hardness, dissolution, and disintegration times. The examiner maintains that it would have been prima facie obvious to one of ordinary skill in the art to have incorporated pregelatinized starch into another oral preparation, such as the lurasidone preparation taught by Fujihara et. al., within the amount taught by Salpekar et. al., for the purpose of improving the dissolution time. The rejection under 35 USC 103(a) as being unpatentable over Fujihara et. al., in view of Salpekar et. al., was proper and is maintained for reasons of record. This rejection will be reiterated in the office action, for Applicant's convenience.

Applicants have requested that the rejection for obviousness type double patenting over the claims of co-pending application 12/997779 be withdrawn, as the instant application is earlier filed. The rejection for obviousness type double patenting is maintained for reasons of record, and will be reiterated in the office action. Accordingly, this action is made FINAL.

2. Claims 1-4, 9, 11-14, 16, 19-34, and 37 were examined.

3. Claims 1-4, 9, 11-14, 16, 19-34, and 37 are rejected.

Claim Rejections-35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-4, 9, 11-14, 16, 19-34, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujihara et. al., EP Patent Publication No. 1327440, in view of Salpekar et. al., US Patent No. 4,600,579 (both of previous record).

The claims are drawn to an oral composition comprised of lurasidone, pregelatinized starch, a water soluble excipient such as mannitol or lactose, and a water soluble polymer binder. The claims are also drawn to the composition in which the pregelatinized starch is present in an amount from 10-50% by weight, and in which the lurasidone is present in an amount from 25 to 45% by weight.

Fujihara et. al. teaches an oral composition comprised of a slightly water soluble active ingredient, such as lurasidone, along with a first disintegrant, a

second disintegrant, and a water soluble polymer binder (Abstract; p. 4-5, paragraph [0008]). Fujihara et. al. teaches that the composition provides advantageous dissolution characteristics when ingested (Abstract). Corn starch is taught and exemplified as a first disintegrant (p. 4, lines 6-9; p. 5, paragraph [0011]; p. 22, paragraph [0152], Ex. 28). It is taught that one of the water soluble excipients includes sugar alcohols such as mannitol or lactose (p. 3, paragraph [0017], item (18); p. 5, paragraph [0014]). The other disintegrant is taught as including excipients such as microcrystalline cellulose, croscarmellose sodium, among others (p. 5, paragraph [0011]), and the water soluble polymer binder includes polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl methylcellulose, and others (p. 4, lines 10-12; p. 5, paragraph [0010]). It is taught that the amount of lurasidone present in the oral composition is 40 mg., which is within the range instantly claimed (p. 5, paragraph [0015]; p. 22, paragraph [0152], Table 28), and that the average particle size of lurasidone is between 0.5 to 5 µm (p. 6, paragraph [0021]). It is taught that for a tablet of a weight of approximately 142 mg., the amount of lurasidone present is 40 mg., which is approximately 28 % of the weight of the composition (p. 29, paragraph [0194], Table 44). The water soluble polymer binder is taught to comprise from about 1 to 10% by weight of the preparation (p. 4, lines 39-40), and water soluble excipients such as mannitol or lactose are taught to comprise from 200 to 2000 % by weight to the weight of lurasidone (p. 9, paragraph [0066]), however, Fujihara et. al. provides an example wherein mannitol is present in an amount of 94 mg., and lurasidone present in an amount of 20 mg. (p. 20, Table 24, paragraph [0145]), in addition to

another example wherein lurasidone comprises 40 mg. of the tablet, while mannitol comprises 132 mg., of a total mass of 250 mg. for the tablet (p. 23, paragraph [0159], Table 32, Ex. 24). Thus, Fujihara teaches a water soluble excipient such as D-mannitol or lactose to comprise about 53% of the tablet (p. 23, paragraph [0159], Ex. 24 of Table 32; 132 mg./250 mg. is about 53%), which is within the amount range of water soluble excipient cited in the claimed composition. Fujihara provides an example formulation wherein the amount of the disintegrant crosscarmellose sodium is 4.8 % of the tablet weight (12 mg. for a 250 mg. tablet; p. 23, paragraph [0159], Table 32); therefore, the limitation of claim 30 is met. It is taught that the oral preparation comprises a granule, which is prepared by granulating the water-soluble polymer binder with the powdery mixture consisting of the active agent (lurasidone), a water soluble excipient, and another disintegrant (p. 3, paragraph [0007], items (11-13); p. 4, paragraph [0007], item (40)). Fujihara et. al. teaches that the preparation can be formulated as pills, granules, fine granules, capsules, tablets, etc. (p. 5, paragraph [0016]).

Fujihara et. al. does not explicitly teach that the composition comprises pregelatinized starch, in an amount from 10 to 50% by weight of the composition. It is not explicitly taught that the composition comprises 80 mg. of lurasidone.

Salpekar et. al. teaches that a composition comprised of a pharmaceutically active ingredient, a lubricant, a disintegrant, and pregelatinized starch allows for high hardness, and short dissolution time when ingested (Abstract). Salpekar et. al. teaches that the composition comprised of the pregelatinized starch is beneficial for preparing oral pharmaceutical formulations

such as tablets (column 1, lines 22-29). It is taught that the partially pregelatinized starch, such as the starch commercially known as Starch 1500, acts as a binder to the composition, and provides beneficial disintegrant properties, as well as increasing hardness of the composition and shortening the dissolution and disintegration time (column 3, lines 38-51; column 4, lines 31-37). Salpekar et. al. teaches that the amount of partially pregelatinized starch ranges from 5 or less to 15 or more parts per 100 parts of the composition (column 4, lines 15-17), which is within the amount of pregelatinized starch instantly claimed. It is taught that the amount of pregelatinized starch present is based upon the amount necessary to impart the high hardness and decreased dissolution times to the composition (column 4, lines 3-9); therefore, it would have been obvious to one of ordinary skill in the art that the optimum range of the pregelatinized starch may comprise amounts greater than or less than 5-15 % by weight, as taught. Salpekar et. al. teaches that the percent gelatinization of the pregelatinized starch ranges optimally from 50 to 75% (column 2, lines 33-55). Additionally, it is taught that Starch 1500 has a moisture content between 3 and 5 % (column 3, lines 38-45).

One of ordinary skill in the art would have been motivated, at the time of the invention, to have prepared the oral lurasidone preparation taught by Fujihara et. al. with incorporation of the pregelatinized starch excipient taught by Salpekar et. al. because Salpekar et. al. teaches that the pregelatinized starch in oral pharmaceutical formulations provides beneficial properties, such as increased hardness of the tablet, decreased dissolution time after ingestion, and short

disintegration time. As such, it would have been prima facie obvious for one of ordinary skill in the art to have prepared the oral lurasidone composition as taught by Fujihara et. al. with the pregelatinized starch excipient as taught by Salpekar et. al. because both Fujihara et. al. and Salpekar et. al. teach pharmaceutical compositions formulated for oral administration, and Salpekar teaches the addition of a pregelatinized starch for improving the dissolution time of the active agent. One of ordinary skill in the art would have been motivated to have incorporated pregelatinized starch, within the amount range as claimed, with a reasonable expectation that the dissolution and solubility of lurasidone HCl would have been improved. Properties associated with a composition are not patentably separable from the composition itself; see MPEP 2141.02, *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). Therefore, as it would have been prima facie obvious to have prepared an oral composition comprised of lurasidone HCl, pregelatinized starch, within the amount ranges as cited, in addition to a water-soluble excipient, it would have been prima facie obvious that properties associated with the composition, such as the similarity factor f2, which is cited as being in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 mg. to 120 mg., a 50% by volume particle size of lurasidone of 0.1 to 8 μm, and an equivalent dissolution profile across the range of lurasidone per oral preparation, would also have been present. Fujihara explicitly teaches oral preparations comprised of lurasidone HCl up to 40 mg.; however, one of ordinary skill in the art would have expected success in incorporating a greater amount of lurasidone HCl in the preparation,

as the pregelatinized starch taught by Salpekar et. al. improves the solubility and dissolution of the drug. It would have been obvious as such to have incorporated 80 mg. to 160 mg. of lurasidone HCl into the oral preparation, with the expectation that the presence of the pregelatinized starch, as taught by Salpekar, would have allowed for effective solubility and dissolution of the drug. Therefore, there would have been an expectation of success in utilizing the pregelatinized excipient for the composition comprising lurasidone, because it is taught by Salpekar et. al. that the pregelatinized starch imparts beneficial properties such as improvement of dissolution and disintegration to oral formulations.

Claim Rejections-Obviousness Type Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-4, 9, 11-14, 16, 19-34, and 37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 12/997779. Although the conflicting claims are not identical, they are not patentably distinct from each other because: the co-pending claims and the instant claims are directed to compositions which overlap considerably in scope. The instantly claimed composition is directed to an oral composition comprised of lurasidone HCl in an amount between 20% to 45% by weight, a pregelatinized starch in an amount from about 10% to about 50% by weight, and a water soluble excipient; the co-pending claims are directed to a tablet comprised of an active ingredient in an amount not less than 25% by weight, mannitol, a pregelatinized starch, and a disintegrant. The claimed

composition also comprises the ingredients cited in the co-pending claims, and as such the claims are not patentably separable.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

10. Claims 1-4, 9, 11-14, 16, 19-34, and 37 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 7:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARAH PIHONAK/
Examiner, Art Unit 1627

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	22381	(pregelatin$6 or (pre-gelatin$6)) adj6 starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:31
L2	3343	((pregelatin$6 or (pre-gelatin$6)) adj6 starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:32
L3	942420	(solubility or dissolution or $4availability or soluble or $4available).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33
L4	1105	l2 and l3	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33
L5	195	lurasidone or latuda	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33
L6	3	l4 and l5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33
L7	1572986	(drug or pharmaceutical or medicine or medicament or active).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:34
L8	719	l4 and l7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:35
L9	64608	(schizophren$2 or psychosis or psychotic or neurological or psychiatric or mental or cognit$3).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:40

EAST Search History (Prior Art)

L10	37	l8 and l9	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:40
L11	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:04
L12	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2012/11/26 11:04
L13	3294	dainippon.as.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:05
L14	1	l2 and l13	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:05
L15	39	l1 and l13	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:05
S1	4	"2001076557".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2009/07/17 07:52
S2	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:53
S3	2622	pre-gelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S4	0	S2 and S3	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S5	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S6	25	S2 and S5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:55

EAST Search History (Prior Art)

S7	234938	oral and pharmaceutical	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S8	10067	S5 and S7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S9	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S10	446	S9 and oral	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:02
S11	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:17
S12	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S13	1	S11 and S12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S14	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S15	86	S11 and S14	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S16	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:57

EAST Search History (Prior Art)

S17	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S18	86	S16 and S17	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S19	1	"3607394".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2009/11/12 14:11
S20	67	(pregelatin$4 with starch) same (polymer with binder)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:29
S21	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S22	745	S21 and (starch adj "1500")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S23	47786	water adj solub$4 adj polymer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40
S24	43	S22 and S23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40
S25	99	S21 and (PCS)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:42
S26	5	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2009/11/12 15:05
S27	4	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2009/11/12 15:07

EAST Search History (Prior Art)

S28	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S29	1747	S28 and (water or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S30	202	S28 with (water or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:15
S31	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2010/07/20 12:22
S32	4	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:23
S33	84	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:24
S34	15801	pregelatin$5 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:25
S35	31	S33 and S34	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:25
S36	23548	accugel or absorbo or actobody or alphajel or allbond or alstar or amaizo or amalean or amerikor or amicoa or amidex or amigel or amilofax or amilys or amisol or amycol or amylex or amylogel or amylogum or amylomaize or amylon or amylose	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:27
S37	0	S33 and S36	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:28
S38	1	"4600579".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/11/02 11:19

EAST Search History (Prior Art)

S39	2	"20040028741".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2012/03/08 12:35
S40	1936	(corn adj starch) with (pregelatinized adj starch)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 13:13
S41	1138	(corn adj starch) adj5 (pregelatinized adj starch)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 13:13
S42	4	"2002053140".pn.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:12
S43	4	"2003066039".pn.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:13
S44	6	"2005009999".pn.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:15
S45	2389	((pregelatinize$1 or pregelatinise$1) adj4 starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:50
S46	16953	((improve$4 or increas$4) adj4 (solubility or soluble)).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:51
S47	41	S45 and S46	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:51
S48	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2012/03/08 16:19
S49	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 16:19
S50	3215	dainippon.as.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:20
S51	232	((pregelatinize$1 or pregelatinise$1) with starch).ab.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:21
S52	1	S50 and S51	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:21

EAST Search History (Prior Art)

S53	1	S48 and S51	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:22

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search in EAST, PALM	11/12/2009	S.P.
Invention and claims search in EAST, STN	11/12/2009	S.P.
Inventor search in EAST, PALM	7/12/2010	S.P.
Invention and claims search in EAST, STN	7/12/2010	S.P.
invention and claims search updated in EAST, STN	3/8/2012	S.P.
updated inventor and assignee search in EAST, PALM	3/8/2012	S.P.
updated inventor and assignee search in EAST, PALM	11/26/2012	S.P.
updated invention and claims search in EAST, STN	11/26/2012	S.P.
STIC search	11/30/2012	S.P.

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/S. P./ Examiner.Art Unit 1627	

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L1            1 S US 20090143404/PN

     FILE 'REGISTRY' ENTERED AT 10:18:20 ON 26 NOV 2012
L2            1 S 9005-25-8/RN

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2012 ACS on STN
RN   9005-25-8  REGISTRY
CN   Starch  (CA INDEX NAME)
OTHER NAMES:
CN   α-Starch
CN   75A
CN   75A (polysaccharide)
CN   Absorbo HP
CN   AccuGel
CN   Ace P 320
CN   Actobody TP 2
CN   ADM Clineo 716
CN   Aeromyl 115
CN   Agglofroid 009
CN   Agglofroid 313E
CN   Allbond 200
CN   Alphajel KS 37
CN   Alstar B
CN   Alstar E
CN   Alstar H
CN   Amaizo 100
CN   Amaizo 213
CN   Amaizo 310
CN   Amaizo 5
CN   Amaizo 71
CN   Amaizo 710
CN   Amaizo W 13
CN   Amalean I-A 2131
CN   Amalean I-A 7081
CN   Amerikor 818
CN   Amicoa
CN   Amidex 3001
CN   Amidex 3005
CN   Amidex 4001
CN   Amido-STA 1500
CN   Amidomax 4800
CN   Amigel
CN   Amigel 12014
CN   Amigel 30076
CN   Amijel VA 160
CN   Amilofaks
CN   Amilofax 00
CN   Amilys 100
CN   Amisol 3408
CN   Amycol HF
CN   Amycol K
CN   Amycol W
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CN   Amylex 20/20
CN   Amylogel
CN   Amylogel 03001
CN   Amylogel 03003
CN   Amylogel HB 450
CN   Amylogum
CN   Amylomaize starch


                SET NOTICE 1 DISPLAY
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     FILE 'REGISTRY' ENTERED AT 10:18:44 ON 26 NOV 2012
                E LURASIDONE/CN

L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2012 ACS on STN
RN   367514-87-2  REGISTRY
ED   Entered STN:  07 Nov 2001
CN   4,7-Methano-1H-isoindole-1,3(2H)-dione,
     2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-
     piperazinyl]methyl]cyclohexyl]methyl]hexahydro-, (3aR,4S,7R,7aS)-  (CA
     INDEX NAME)
OTHER NAMES:
CN   (3AR,4S,7R,7aS)-2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)piperazin-1-
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CN   2-[[(1R,2R)-2-[[4-(1,2-Benzoisothiazol-3-yl)-1-
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methano-
     1H-isoindole-1,3(2H)-dione
CN   Latuda
CN   Lurasidone
FS   STEREOSEARCH
MF   C28 H36 N4 O2 S
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ANABSTR, CA, CAPLUS, CASREACT, CBNB, CHEMCATS,
       CHEMLIST, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, TOXCENTER,
USAN,
       USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
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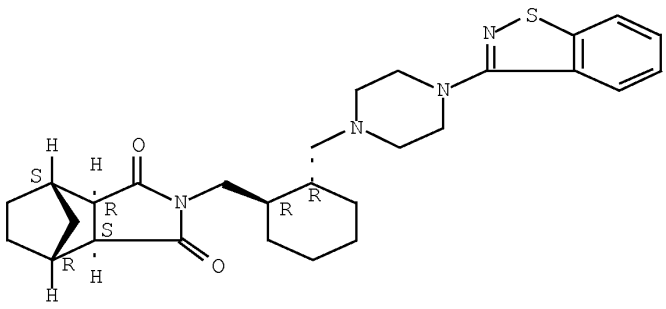

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L3 1 S E3

FILE 'CAPLUS' ENTERED AT 10:19:16 ON 26 NOV 2012
L4 138787 S L2
L5 77 S L3
L6 2 S L4 AND L5
L7 1 S L6 NOT L1

L7 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2012 ACS on STN
AB The invention discloses to a lurasidone coating tablet which contains 0.1-8mm lurasidone hydrochloride(structural formula provided on page 2) 10-50, cellulose derivative(low substituted HPC) 15-50, sugar alc. 5-50, filler 5-50, adjuvants(binder, lubricant, or glidant) 1-20 weight%. The sugar alc. is mannitol, lactose, sorbierite, sucrose, fructose preferably mannitol or lactose; the filler is starch, dextrin, microcryst. cellulose, or modified starch; the binder is water-soluble polymer; the lubricant is Mg stearate, stearic acid, Zn stearate, liquid paraffin, PEG, and/or hydrogenated vegetable oil; the glidant is SiO2, colloidal silicon dioxide, silica gel micropowder, and/or talc powder. The preparation process comprises uniformly mixing lurasidone hydrochloride, sugar alc. and part or whole of low substituted HPC, wet granulating using water or <40% ethanol as wetting agent or using binder solution, drying, adding residual low substituted HPC(if presence), optional lubricant and glidant, mixing uniformly, tableting, and optionally coating to obtain the lurasidone coating tablet. The content of lurasidone in coating tablet is 10-160mg per tablet. The lurasidone coating tablet has good drug release performance and good mech. property.
ACCESSION NUMBER: 2012:1419908 CAPLUS Full-text
DOCUMENT NUMBER: 157:558467
TITLE: Lurasidone coating tablet and preparation method thereof
INVENTOR(S): Li, Xinghui
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 10pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 102688209	A	20120926	CN 2012-10206844	20120621
PRIORITY APPLN. INFO.:			CN 2012-10206844	20120621

```
                E PHARMACEUTICAL TABLETS/CT
                E E15+ALL/CT
L8         73330 S E34-E35,E41-E42,E44,E53
                E DISSOLUTION/CT
                E E56+ALL/CT
L9         68521 S E67-E68
L10         8592 S L4 AND L8
L11         3243 S L4 AND L9
L12            0 S L4 (L) L9
L13         3243 S L4 (S) L9
L14            0 S L4 (L) L8
L15         9098 S L8 AND L9
L16         1864 S L4 AND L15
L17        62093 S (?ENHANC? OR ?IMPROV? OR ?INCREAS?)(S)(?DISSOL?)
L18          253 S L16 AND L17
L19           39 S L18 AND (PY<=2006 OR PRY<=2006 OR AY<=2006)
L20           38 S L19 NOT L1
L21           38 S L20 NOT L7
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/13/2009	07/20/2010	03/08/2012	12/06/2012					
	1	✓	✓	✓	✓					
	2	✓	✓	✓	✓					
	3	✓	✓	✓	✓					
	4	✓	✓	✓	✓					
	5	N	N	N	N					
	6	N	N	N	N					
	7	N	N	N	N					
	8	✓	-	-	-					
	9	✓	✓	✓	✓					
	10	✓	-	-	-					
	11	✓	✓	✓	✓					
	12	✓	✓	✓	✓					
	13	✓	✓	✓	✓					
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	30			✓	✓					
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	33			✓	✓					
	34			✓	✓					
	35			N	N					
	36			N	N					

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/13/2009	07/20/2010	03/08/2012	12/06/2012					
	37				✓					

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11919678	Filing Date	2007-10-31	Docket Number (if applicable)	7379/98100	Art Unit	1627
First Named Inventor	Kazuyuki FUJIHARA			Examiner Name	Sarah PIHONAK		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☒ Other
Petition For Extension of Time

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 061135

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	/Kendrew H. Colton/	Date (YYYY-MM-DD)	2013-06-11
Name	Kendrew H. Colton	Registration Number	30368

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
Kazuyuki FUJIHARA	:	Confirmation No.: 6965
U.S. Application No.: 11/919,678	:	Examiner: PIHONAK, SARAH
Filed: October 31, 2007	:	Group Art Unit: 1627
	:	Attorney Docket No.: 7379/98100

For: PHARMACEUTICAL COMPOSITION

AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Kindly enter this Amendment and grant the concurrently filed Petition for Extension of Time. This Amendment should be considered together with the concurrently filed Appendix.

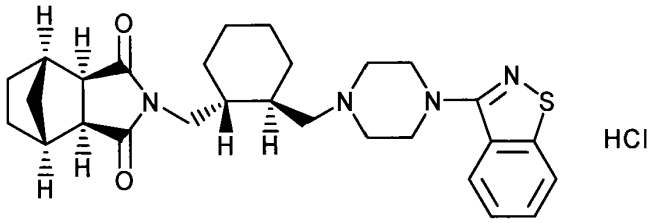
TABLE OF CONTENTS

Amendments to the Claims:

This listing of claims replaces any and all prior claim lists.

Listing of Claims:

1. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

2. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

3. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder;

wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

4. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose.

5. (Withdrawn) A method for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder.

6. (Withdrawn) A method for preparing the oral preparation of claim 1 wherein the method comprises granulation of a powder mixture which comprises granulating a powder mixture comprising a pregelatinized starch and a water-soluble excipient by using a solution or dispersion of lurasidone and a water-soluble polymer binder.

7. (Withdrawn) The method of claim 5 wherein the water-soluble excipient is mannitol or lactose.

8. (Canceled)

9. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10. (Canceled)

11. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

12. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. (Canceled)

16. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17-18. (Canceled)

19. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

20. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Previously Presented) The oral preparation of claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Previously presented) The oral preparation of claim 1 wherein a 50% by volume particle size of lurasidone is 0.1 to 8 μm.

23. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

25. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 20 to 45% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

26. (Previously Presented) The oral preparation of claim 9 wherein the water-soluble excipient is mannitol or lactose.

27. (Previously submitted) The oral preparation of claim 1 wherein a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt).

28. (Previously submitted) The oral preparation of claim 1 wherein the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose.

29. (Previously submitted) The oral preparation of claim 1 wherein a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

30. (Previously submitted) The oral preparation of claim 1, further comprising a disintegrant wherein a content of the disintegrant per tablet is 0.5 to 5% (wt/wt).

31. (Currently amended) The oral preparation of claim 1, further comprising a disintegrant wherein

a content of the disintegrant per tablet is 0.5 to 5% (wt/wt);

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation;

a content of lurasidone per tablet is 40 to 120 mg;

a pregelatinizing ratio of the pregelatinized starch is 50 to 95%;

50% by volume particle size of lurasidone is 0.1 to 8 μm;

the pregelatinized starch contains water soluble matter of 30% or less;

a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt);

the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose; and

a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

32. (Previously submitted) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 160 mg.

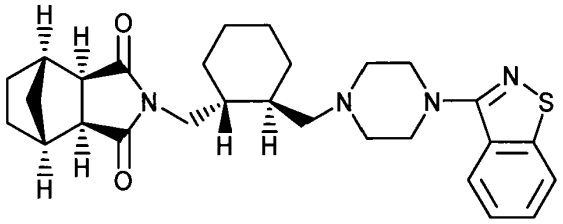
33. (Previously submitted) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 80 to 160 mg.

34. (Previously submitted) The oral preparation of either one of claim 1 or 31, wherein a similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg.

35. (Withdrawn) A method for treating psychosis, comprising administering the oral preparation of claim 1 to a patient suffering from psychosis.

36. (Withdrawn) A method for treating schizophrenia, comprising administering the oral preparation of claim 1 to a patient suffering from schizophrenia.

37. (Previously presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, wherein the oral preparation contains 20 to 45% (wt/wt) of lurasidone, the oral preparation contains 20 mg to 120 mg of lurasidone, the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the oral preparation, and the oral preparation exhibits an equivalent dissolution profile across the range of lurasidone per oral preparation.

38. (New) The oral preparation of either one of claim 1 or 31, wherein the water-soluble excipient is one or more selected from the group consisting of mannitol, lactose, saccharose, sorbitol, D-sorbitol, erythritol and xylitol.

39. (New) The oral preparation of either one of claim 30 or 31, wherein the disintegrant is one or more selected from the group consisting of corn starch, crystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium and crospovidone.

REMARKS

Applicant courteously solicits favorable reconsideration upon entry of this Amendment and consideration of the concurrently filed Appendix (evidence).

Claims Presented

Upon entry of this Amendment claims 1-7, 9, 11-14, 16, and 19-39 are presented. Claims 5-7 and 35-36 are withdrawn.

The new and amended claims avoid new matter and entry thereof is courteously solicited. Claim 31 is amended to correct "article" to "particle." New claims 38 and 39 find basis in the original specification at paragraphs [0017] and [0020], respectively.

Rejoinder is requested.

Applicant respectfully solicits rejoinder of the withdrawn claims 5-7 and 35-36.

Claims 1-4, 9, 11-14, 16, 19-34 and 37 define unobvious inventions over Fujihara and Salepakar. Even if combined, the references would not have suggested these claimed inventions.

Applicants respectfully traverse the rejection of claims 1-4, 9, 11-14, 16, 19-34 and 37 under 35 U.S.C. §103(a) over Fujihara *et al.* (EP Patent Publication No. 1327440) in view of Salpekar *et al.* (U.S. Patent No. 4,600,579).

Introducing the claims inventions versus the references.

Aspects of the present claimed inventions involve an oral preparation that can comprise higher contents of a hardly-soluble pharmaceutically active agent (e.g. lurasidone), yet the preparation exhibits a similar dissolution profile as compared to oral preparations having different contents of such pharmaceutically active agent (*see, e.g.,* specification, paragraphs [0001], [0008]-[0009] and [0013]; the examples and FIG. 3.).

Applicant has found that it is possible to provide an oral preparation having a lurasidone content in the preparation of 20 to 45% (wt/wt.) in combination with 10 to 50% (wt/wt) pregelatinized starch that provides advantageous dissolution profiles.

More particularly, characteristics of the present invention include:

1) the oral preparation of the present invention includes a high lurasidone content per tablet, particularly high content ratio (%) of 20 to 45% (wt/wt) of lurasidone as recited in claim 1 - which allows the employment of relatively high total amounts of lurasidone in a tablet of relatively small size – while, at the same time, the oral preparation exhibits beneficial dissolution properties (*see, e.g.,* paragraph [0106]);

2) the oral preparation of the present invention incorporates pregelatinized starch in a range of 10 to 50% (wt/wt) based on the weight of the preparation; and

3) the preparation of the present invention has beneficial dissolution properties, that is, it shows equivalent dissolution profiles as between oral preparations having different contents of lurasidone, as reflected by a similarity factor (f2) of $\geq$ 50[1], and furthermore exhibits rapid dissolution (*e.g.,* a dissolution of at least 85% of the initially present lurasidone within 30 minutes).

In short, an oral preparation provides a high content ratio of lurasidone (which allows employing comparatively higher amounts of lurasidone in relatively small tablets) that, at the same time, exhibiting rapid dissolution. Oral preparations having different lurasidone contents exhibit equivalent dissolution profiles ($f2 \geq 50$). This is a distinct advantage. This combination of advantageous properties results from the presence of pregelatinized starch in the claimed oral preparation in an amount of 10 to 50% (wt/wt) based on the weight of the preparation, as can be seen from the data shown in the as discussed in this Amendment.

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[1] Dependent claim 34 provides an oral preparation according to claim 1 or 31 has a similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg. *Neither* cited reference describes or suggests claim 34.

None of the prior art documents applied against the claims would have taught or suggested this oral preparation or its advantages.

As demonstrated below, Fujihara (the primary reference) does not teach or suggest an oral preparation which contains lurasidone in a content ratio of lurasidone of 20 to 45% (wt/wt)) (claims 1, 2 and 3) that can include, for instance, 20 mg to 120 mg lurasidone per oral preparation (dependent claim 13, independent claim 37), is completely silent on the use of pregelatinized starch, does not teach or disclose a pregelainized starch in an amount of 10 to 50% (wt/wt) based on the weight of the preparation (independent claims 1, 2, 3, and 37), and does not disclose or teach an oral preparation with the superior dissolution properties obtainable with a present oral preparation, such as equivalent dissolution profiles at different contents of lurasidone[2] (*see, e.g.,* claim 37), as reflected by a similarity factor (f2) of $\geq$ 50 (note dependent claim 34), and also rapid dissolution (*e.g.,* a dissolution of at least 85% of the initially present lurasidone within 30 minutes).

As also demonstrated below, these and other shortcomings of Fujihara would not have been overcome even if, for the sake of argument, Fujihara is additionally combined with Salpekar, which combination would not have been made in any event.

Salpekar's compositions containing the comparatively water soluble acetomimophen are not apposite to the present oral preparations containing the comparatively water insoluble lurasidone, are not relatable except with hindsight to Fujihara, do not teach or even suggest any lurasidone oral preparation, and when fairly considered teach away the incorporation of the comparatively larger amount of the pregelatinized starch into an oral preparation because of undesirable disintegration times. In other words, there would have been no expectation of achieving the present claimed oral preparations and their advantages.

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[2] *In re Papesch*, 137 U.S.P.Q 143 (CCPA 1963).

Therefore, *even if* Fujihara were combined with Salpekar, which is a point not conceded, the present claimed oral preparations with their advantages would have been *un*foreseen and *un*expected by a person skilled in the art.

Fujihara does not teach or suggest the pregelatinzed starch in the claims.

Claim 1 refers to an oral preparation containing "a pregelatinized starch, ...wherein ... the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation." *See also* independent claims 2, 3 and 37.

Dependent claim 9 refers to an oral preparation wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation. *See also* dependent claims 19, 20, 24, 25, and 31.

Fujihara is completely silent on the use of pregelatinized starch or on the advantages to an oral preparation having the pregelatinized startch incorporated in an amount of 10 to 50% (wt/wt).

Accordingly, the advantageous dissolution profiles for a present oral preparation having a higher content ratio of lurasidone (*see, e.g.,* Applicant's prior Amendment) with the recited amount of pregelatinized starch, is neither taught nor suggested by Fujihara.

Fujihara's shortcomings are not overcome, even if, for the sake of argument it were combined with Salpekar, which is a combination that would *not* have been made by a person of ordinary skill in the art.

Fujihara in view of Salpekar nonetheless would not have provided motivation towards the claimed inventions.

As demonstrated below, this follows since Salpekar teaches a specific composition comprising acetaminophen as the pharmaceutically active ingredient and pregelatinized starch, which is significantly more water soluble compared to the

chemically different and relatively water insoluble lurasidone, and even if *arguendo* some of Salpekar's acetaminophen-containing compositions having other additives and amounts may allow a shorter dissolution time and may shorten the dissolution and disintegration time.

None-the-less, the Examiner has alleged that Salpekar teaches that the amount of pregelatinized starch ranges from 5 or less to 15 or more parts per 100 parts of the composition (e.g. Office Action, page 4 lines 20-22). Applicant respectfully disagrees and requests reconsideration.

Even if, for the sake of argument, the Examiner's acknowledgement might be correct, which is a point not conceded, and even if the two references would have been combined, which is another point not conceded, in order to arrive at the present claimed invention, a person of ordinary skill in the art would have been required to combine Fujihara disclosing lurasidone oral preparations, while ignoring Salpekar's teachings to use acetaminophen, with Salpekar disclosing pregelatinized starch, and further, adopt the amount of pregelatinized starch (i.e. 20 to 30% (wt/wt)) which is beyond the range of 5 to 15 parts disclosed in Salpekar and beyond 18.0% in Example 1 which is unfavorable in view of the disintegration time.

Selpekar teaches away from the pregelatinized starch in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

Claim 1 recites "the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation."

Salpekar effectively teaches away from this feature in claim 1 and other claims 2, 3, and 37 as examples.

First, Sepekar teaches that only a combination of small amounts of pregelatinzed starch ("PGS"), such as 8.85 % or 6.4%, and at least an auxiliary binder disclosed can improve disintegration time in the acetaminophen tablets. Sepekar's disclosed value of 8.85% or 6.4% would not have suggested an oral composition containing lurasidone and

pregelatinized starch incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

Second, Salpekar's Examples and related disclosures show that larger amounts of pregelatinized starch, such as the 18.0% in Example 1, do not improve the disintegration time and the dissolution profile of the acetaminophen-containing tablet.

The poorer results reported with 18% pregelatinized starch would have led away from claim 1. More particularly, Salpekar's Examples 1-3 are teach away from the amount of pregelatinized starch in the present claims.[3] From the Table in column 8 and taking col. 4, lines 3-9 into consideration, the Example 1 tablet (18.0% of PGS) is not acceptable in order to solve Salpekar's problem, since the disintegration time of Example 1 tablet is 18.0 minutes which is 300% times longer than that the Example 2 tablet (6 minutes) and 1200% times longer than the Example 3 tablet (1.5 minutes). Even the Example 2 tablet comprising 8.85% of PGS is more disadvantageous since it shows a 400% times longer disintegration time than exhibited by a tablet according to Salpekar's Example 3.

Thus, a present oral preparation having pregelatinized starch incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation would not have been suggested by the poorer results reported for Sepekar's Example 3 (18% of PGS) (*e.g.*, an increased disintegration time for the acetaminophen containing composition). Increasing the amount of pregelatinized starch would have suggested longer, not shorter disintegration times in an acetominophen tablet, but longer disintegration times would have been contrary to Salpekar's stated objective for disintegration times (col. 4, lines 3-9).

Third, even if, for the sake of argument, Salpekar *et al.* were combined with Fujihara, a person skilled in the art would not have arrived at the pregelatinized starch

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[3] Salpekar explains at column 8, lines 44-49 that "As indicated in these examples, Example 1 contains neither auxiliary binder nor auxiliary disintegrating agent; Example 2 includes an auxiliary binder but no auxiliary disintegrating agent; and Example 3 includes both an auxiliary binder and an auxiliary disintegrating agent."

(10 to 50% (wt/wt)) in the independent claims. Those skilled in the art would have understood from Salpekar that 4.45-8.85% of pregelatinized starch is preferable for an acetaminophen tablet having a short disintegration time and a short dissolution time. Although Salpekar might be said to teach an effective amount of pregelatinized starch (PGS) is from about 5 or less to about 15 or more parts per 100 parts of the acetaminophen composition (*see*, col. 4, lines 15-17), Salpekar's acetaminophen compositions that show technical effects are only those supported by Examples 2 and 3 (*i.e.*, 4.45-8.85% of pregelatinized starch). This follows from Salpekar's disclosure that the pregelatized starch is included in an amount effective for imparting to the acetaminophen composition the capability of being formed into tablets having high hardness, short disintegration time (*e.g.*, about 10 minutes or less) and short dissolution time (e.g., about 20 minutes or less). *See*, col. 4, lines 3-9. In other words, Fujihara + Salpekar, even if the combination were made, which is not conceded, a person of ordinary skill in the art would have been led away from the claimed oral preparations.

Contrary to the Office Action, Salpekar actually teaches away from the present claimed inventions.

In response to Applicant's previous argument against Salpekar regarding a comparison of Examples 1 and 2, the Examiner asserts that the disintegration profile comparison of the examples referred to by Salpekar shows the differences in the compositions with and without an auxiliary binder and auxiliary disintegration agent. See, Office Action, page 8 lines 14-17.

In this respect, although Applicant argued that Example 1 of Salpekar which includes 18.0% of pregelatinized starch should not be preferable in view of longer disintegration time of 18.0 minutes in Example 1 compared to shorter disintegration time of 6 or 1.5 minutes in Example 2 or 3, which constitutes a "teaching-away" factor for high content ratios of pregelatinized starch comprised in a composition such as 18.0% in Example 1 of Salpekar, the Examiner asserts that Salpekar teaches that the

composition comprised of the pregelatinized starch is beneficial for preparing oral pharmaceutical formulations with high hardness and short dissolution time. See Office Action, page 12 line 19 to page 13 line 5, etc.

However, Applicant disagrees with the Examiner's acknowledgement.

As evident, Salpekar discloses that an additional binding agent (referred to as a "compressibility-promoting agent") such as PVP may be included in the composition in order to increase the obtainable hardness of tablets. See, Salpekar, column 4 line 67 to column 5 line 3. An additional disintegration agent (referred to as a "disintegration-promoting material"), such as XL-PVP, may be included in the acetaminophen composition to decrease the obtainable disintegration time of tablets. See, Salpekar column 5 lines 24 to 29.

Specifically, Salpekar's Example 1 discloses its composition comprises neither an additional binding agent nor an additional disintegration agent, whereas Salpekar's Example 2 does not comprise XL-PVP as the additional disintegration agent but comprises PVP as the additional binding agent. Consequently, when the compositions of Examples 1 and 2 are compared, a person of ordinary skill in the art would expect the composition of Example 2 comprising the additional binding agent to increase the hardness of tablets, and Example 2 actually shows 13 kp of hardness which is higher than Example 1 (9.3 kp).

Typically, in the art it has been believed that a binding agent makes a disintegration time of composition longer in view of the increase of hardness. Nevertheless, Example 2 shows 6 minutes of the disintegration time which is one-third of the disintegration time of Example 1 (18.0 minutes). Then, a skilled person would consider that the reason why Example 2 - even comprising the binding agent - could achieve a shorter disintegration time is to reduce the amount of pregelatinized starch by more than half in Example 2 (i.e. from 18.0% of Example 1 to 8.85% of Example 2),

which is the only difference between Examples 1 and 2 except for the inclusion of the binding agent in Example 2.

As seen in abstract, the Salpekar acetaminophen composition should achieve a tablet having both (1) high hardness, and (2) short disintegration time and short dissolution time, where the property (1) and the property (2) are clearly an opposite property each other. In view of this technical goal in Salpekar and the above comparison between Examples 1 and 2, Example 1 could not meet the two properties since the disintegration time of Example 1 was 18.0 minutes which is apparently longer than "short disintegration time" (i.e. 10 minutes or less). See, Salpekar, col. 4 lines 3-9.

As mentioned above, the only difference between Examples 1 and 2 is that Example 2 comprises only less than half of pregelatinized starch in Example 1 except for the inclusion of PVP in Example 2 which basically increases the hardness, then is expected to extend the disintegration time. That means that Salpekar discloses that only 4.45 to 8.85% of pregelatinized starch could work for achieving the tablet having the desired above two properties, and a high content ratio of pregelatinized starch such as 18.0% could not achieve the desired tablet.

In short, Salpekar clearly teaches away from Applicant's lurasidone composition having a high content ratio of pregelatinized starch, and certainly teaches away from one having 18.0%.

Literature reports pregelatinized starch (PGS) in amounts that would have taught away from the claimed oral preparation having 10 to 50% (wt/wt) of pregelatinized starch. The literature reports typically 10% or less of PGS as does Salpekar.

The conventional teachings would have led away from the present oral preparations. As reported in the present specification, pregelatinized starch "is often used, typically, in 10% *or less* of contents as described in Non-patent Document 1." *See, e.g.,* specification, paragraph s [0006] and [0007] (emphasis added). *See also,* Applicant's *previously* filed Appendix at item 2. This supports the point that typically

(conventionally) *less* than 10% (wt/wt) pregelatinized starch would have been used, which is consistent with the results Selpaker disclosed for the acetaminophen compositions.

The Office Action has not adduced evidence relating the comparatively water soluble acetoaminophen to the comparatively water insoluble lurasidone. Sepekar discloses acetaminophen. It is markedly much more water soluble than the comparatively water insoluble lurasidone. Therefore, Sepekar's results with only acetaminophen would not have led one to expect the present results obtained with the comparatively water *in*soluble ingredient (lurasidone), nor led to combining Fujihara with Sepekar.

Salpekar exclusively focuses on the comparatively water soluble acetaminophen[4] would not have motivated a person of ordinary skill in the art would towards an oral preparation having 10 to 50% (wt/wt) of pregelatinized starch and the comparatively water *in*soluble lurasidone as recited in the claims.

There is no evidence cited in the Office Action to show a person of ordinary skill in the art would have related acetaminophen with lurasidone, nor is there evidence cited to suggest Sepekar's results with the former would have led to a candidate of choice to be selected in discovering an oral preparation as claimed. The compounds are different. Their properties are different.

The Examiner, however, isolates and cites passages in Salpekar at col. 3, lines 46-51 and col. 4, lines 31-37, see, e.g., Office Action, page 5, lines 6-9 from the bottom, as if these passages were generic, which they are not. See, *In re Wesslau*, 147 USPQ 391, 393 (CCPA 1965) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the

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[4] Contrary to the Office Action, Salpekar specifically and only focuses on the requirements for an acetaminophen composition. Selpekar "relates to an N-acetyl-p-amino-phenol composition" (col. 1, lines 6-7) in which "N-acetyl-p-aminophenol [is] ... hereinafter referred to sometimes as acetaminophen..."). Selpekar, col. 1, lines 11-12.

exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.")

Contrary to the Office Action, the actual passages in Salpekar specifically only relate to "the composition," which must contain acetaminophen. *See, e.g.*, Selpekar, Abstract, col. 1, lines 6-29, col. 1, lines 38 and 63, col. 2, line 21, col. 5, line 48, col. 6, (Tables), and the Examples.

Since Salpekar relates only to a comparatively soluble agent "acetaminophen," not to the hardly-soluble agent (lurasidone) in the claimed oral preparations, it would have been ***un***reasonable to expect Salpekar's disclosure regarding an acetaminophen composition to be appropriate for an oral preparation having a "content of [the comparatively hardly soluble] lurasidone ... [of] 20 to 45% (wt/wt)," as claimed herein.

In other words, on the present factual record, there would have been no basis to have expected Selpekar's results with acetaminophen, which is a comparatively more water soluble agent would even have made Salpekar the candidate of choice for, let alone applicable, to a lurasidone composition as in Fujihara since lurasidone is comparatively significantly more water *in*soluble because it is 1/62.5 as soluble as acetaminophen.[5]

Salpekar teaches amounts of a water soluble active ingredient that would not have suggested the amounts of a relatively water *in*soluble active ingredient (lurasidone) in the present oral compositions.

The higher contents of the different material in Salpekar teach away from the claim 1 oral preparation with an oral preparation having "a content of lurasidone in the preparation [of] 20 to 45% (wt/wt)" as in claim 1, as an example.

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[5] Acetaminophen has an experimental water solubility of 14 mg/mL (DrugBank (http://www.drugbank.ca/drugs/DB00316), see the attachment to prior Amendment).

Lurasidone, however, has a water solubility of only 0.224 mg/mL at 20°C, which more than an order of magnitude less than that for acetaminophen.

Salpekar discloses a preferred embodiment is a composition comprising 93-83% of acetaminophen (see line 63, column 5 to line 9, column 6). Those skilled in the art would have had no expectation or motivation to apply Salpekar's formulation for acetaminophen with extremely high contents (93-83%) of that active ingredient to tablets comprising the comparatively water *insoluble* lurasidone in order to solve the problem of the undesired dissolution profiles of lurasidone in a conventional composition.

Commercial success favors patentability for the present claimed inventions.

Applicant respectfully invites the Examiner to peruse the Appendix hereto.

Applicant respectfully submits the great commercial success achieved by the attainment of the oral preparation. This evidence supports unobviousness. The oral preparation comprises high content ratios of lurasidone as the active ingredient and shows a prominent dissolution profile.

The oral lurasidone preparation was approved as LATUDA® in October 2010 by the FDA and in June 2012 by Health Canada, and is currently available for sale as one of therapeutic agents for schizophrenia (tablet) in the U.S. and Canada.

Applicant encloses a News Release of Sunovion (page 3, 5th paragraph), http://www.ds-pharma.com/pdf_view.php?id=299. The Examiner is invited to peruse businesswire. See http://www.businesswire.com/news/home/20130520006314/en.

The Examiner is advised that sales of lurasidone (for present purposes, the above mentioned LATUDA® brand product) in North America reached about $202 million in fiscal year 2012 (from April 2012 to March 2013). Applicant encloses an extract from the Financial Results for FY2012 (5th slide), although the Examiner may wish to peruse http://www.ds-pharma.com/pdf_view.php?id=296.

Applicant traverses the common law obviousness type double patenting rejection. Applicant requests reconsideration and withdrawal of same.

Applicant respectfully requests the Examiner to reconsider the non-statutory rejection of claims 1-4, 9, 11-14, and 19-34 over commonly owned U.S. application 12/997779 and claims 1-8 therein. This application is the earlier filed application (series "11" application) and the common law rejection over claims in a later filed application seems misplaced, and besides, such claims might be canceled or amended, or other action taken. Withdrawal of this non-statutory rejection seems appropriate and is respectfully requested.

Conclusion

Applicant respectfully submits claims 1-4, 9, 11-14, 16, 19-34, 37, and new claims 38-39 are in allowable form. Applicant courteously solicits a Notice of Allowance for these claims.

Applicant respectfully solicits rejoinder for the non-elected claims. If not rejoined, the Examiner is invited to telephone the undersigned regarding disposition of such claims upon allowability for the elected claims.

The Examiner is cordially invited to telephone the undersigned with any comments, suggestions or questions, or to schedule an interview.

Applicant hereby requests that any concurrent or future reply submitted by Applicants to the U.S. Patent and Trademark Office in connection with the above-identified patent application requiring an extension of time under 37 C.F.R. §1.136(a) for its timely submission be treated as incorporating therein a request for an extension of time for the appropriate length of time. In addition, to the extent necessary during prosecution of the present application, Applicant hereby authorizes the Commissioner to charge any required fee not otherwise provided for, including application processing, extension, and extra claims fees, to Deposit Account No. 06-1135 with reference to Attorney Docket No. **7379/98100**.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

/Kendrew H. Colton/

Kendrew H. Colton
Registration No. 30,368
Tel: (202) 419-7000
Fax: (202) 419-7007

Please send official correspondence to:
Customer Number 42798

FITCH, EVEN, TABIN & FLANNERY
1120 20th St., NW, Suite 750 South
Washington, DC 20036

APPENDIX

Sunovion Pharmaceuticals Inc.
84 Waterford Drive, Marlborough, MA 01752-7010
Tel 508-481-6700

SUNOVION

News Release

Contact: Patricia Moriarty
Senior Director, Corporate Communications
Sunovion Pharmaceuticals Inc.
508-787-4279
patricia.moriarty@sunovion.com

Sunovion Pharmaceuticals Inc. Announces Data Showing Latuda® (lurasidone HCl) was Associated with Low Rates of Weight and Metabolic Changes in Patients with Depressive Episodes Associated with Bipolar I Disorder

A Similar Pattern of Metabolic Changes was Observed in Patients Who Received LATUDA as Monotherapy or as Adjunctive Therapy to Mood Stabilizers

Marlborough, Mass., May 20, 2013 – Sunovion Pharmaceuticals Inc. today announced it will present 18 research posters on Latuda® (lurasidone HCl), an atypical antipsychotic indicated for the treatment of adult patients with schizophrenia, at the 166th Annual Meeting of the American Psychiatric Association (APA) in San Francisco. The presentation includes results from analyses of two pivotal studies in patients with depressive episodes associated with bipolar I disorder (bipolar depression). These new data showed that LATUDA in the treatment of bipolar depression, either as monotherapy or added to ongoing treatment with lithium or valproate, was associated with low rates of change in weight, body mass index (BMI), lipid parameters and measures of glycemic control.

The two pivotal studies evaluated the efficacy and safety of LATUDA as monotherapy (PREVAIL 2) or adjunctive therapy (PREVAIL 1) for the treatment of bipolar depression, and supported two supplemental New Drug Applications (sNDAs) that were accepted by the U.S. Food and Drug Administration (FDA) on October 30, 2012.

"Sunovion is pleased to present data from two extensive research programs that studied LATUDA in patients with schizophrenia and bipolar depression," said Antony Loebel, M.D., Executive Vice President and Chief Medical Officer of Sunovion Pharmaceuticals Inc. "We are proud of the contributions we are making to improved understanding of these disorders where high unmet clinical needs remain."

Effects of LATUDA on Metabolic Indices in Bipolar Depression

The LATUDA monotherapy (PREVAIL 2) and adjunctive therapy studies (PREVAIL 1) were six-week, randomized, double-blind, placebo-controlled clinical trials that evaluated the efficacy and safety of LATUDA as monotherapy (20-60 mg/day or 80-120 mg/day vs. placebo, N=505) or adjunctive therapy (20-120 mg/day, N=348) to lithium or valproate in patients with bipolar depression, with or without rapid cycling (DSM-IV-TR). Changes from baseline to Week 6 in metabolic parameters [lipids, glucose, weight,

insulin and homeostatic model assessment of insulin resistance (HOMA-IR)] were assessed [using rank ANCOVA (LOCF) controlling for the baseline values of these metabolic parameters]. Results from the studies were as follows:

PREVAIL 2 (Monotherapy)

- Mean weight change from baseline for LATUDA vs. placebo was 0.64 vs. -0.09 lbs. (p=not significant).
- Weight gain from baseline (≥ 7%) occurred in 2.4% of patients treated with LATUDA vs. 0.7% of patients treated with placebo.
- Mean changes from baseline in metabolic laboratory parameters were: cholesterol -1.7 vs. -3.2 mg/dL, LDL -2.7 vs. -3.5 mg/dL, triglycerides 3.0 vs. 6.0 mg/dL, glucose 0.5 vs. 1.8 mg/dL, insulin 3.56 vs. 2.95 mU/L and HOMA-IR 1.08 vs. 1.19, for LATUDA vs. placebo, respectively (p=not significant for all comparisons).

PREVAIL 1 (Adjunctive Therapy)

- Mean weight change from baseline for LATUDA vs. placebo was 0.51 vs. 0.31 lbs. (p= not significant).
- Weight gain from baseline (≥ 7%) occurred in 3.1% of patients treated with LATUDA vs. 0.7% of patients treated with placebo.
- Mean changes from baseline in metabolic laboratory parameters were: cholesterol -3.0 vs. -3.8 mg/dL, LDL -3.2 vs. -2.0 mg/dL, triglycerides 9.0 vs. -6.2 mg/dL, glucose 0.9 vs. -0.3 mg/dL, insulin 1.66 vs. -0.16 mU/L and HOMA-IR 0.26 vs. -0.07, for LATUDA vs. placebo, respectively (p=not significant for all comparisons).

Using the National Cholesterol Education Program (NCEP) adult treatment panel criteria for metabolic syndrome, approximately 15% of patients met criteria for metabolic syndrome (MetS) at study baseline, which is associated with risk for diabetes and cardiovascular disease.

"Prior research has shown that patients with bipolar disorder are already at high risk for metabolic syndrome," said Loebel. "As such, it is critically important that we continue to evaluate the effect of LATUDA on these key measures of metabolic health, in both short and longer-term treatment."

In PREVAIL 1, the most frequently reported adverse events were nausea, somnolence, tremor, akathisia and insomnia. Discontinuation rates due to adverse events were 6% for LATUDA and 7.9% for placebo. In PREVAIL 2, the most frequently reported adverse events were nausea, headache, akathisia, somnolence and sedation. Discontinuation rates due to adverse events were 6% for LATUDA (either dose group) and 6% for placebo.

About Bipolar I Disorder and Bipolar Depression

Bipolar disorder, a mental illness characterized by debilitating mood swings, affects approximately 10.4 million American adults.[1,2] Bipolar depression refers to the depressive phase of bipolar disorder.[3] Symptoms of bipolar depression include: extreme sadness, anxiety, fatigue, inactivity and disinterest in usual activities, disruptions to sleeping patterns and hopelessness.[1,4] When symptomatic, most people with bipolar disorder tend to be depressed, rather than manic.[3] Bipolar disorder can also double a person's risk of early death from a range of medical conditions, including obesity, diabetes and

cardiovascular disease.[5,6,7] Bipolar disorder is the sixth leading cause of disability worldwide[8] and is among the top 10 leading causes of disability in the United States (U.S.).[9]

About LATUDA

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in five six-week controlled studies of adult patients with schizophrenia. The effectiveness of LATUDA for longer-term use, that is, for more than six weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

The recommended starting dose for LATUDA for the treatment of patients with schizophrenia is 40 mg once daily taken with food (at least 350 calories) with no initial dose titration required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 160 mg/day. The maximum recommended dose is 160 mg/day. For patients with moderate and severe renal or hepatic impairment, the recommended starting dose of LATUDA is 20 mg/day. The maximum recommended dose is 80 mg/day in patients with moderate hepatic impairment and 40 mg/day in patients with severe hepatic impairment. The recommended starting dose of LATUDA in patients taking a moderate CYP3A4 inhibitor such as diltiazem is 20 mg/day with a maximum recommended dose of 80 mg/day. LATUDA should not be administered with strong CYP3A4 inhibitors such as ketoconazole or strong CYP3A4 inducers such as rifampin.

Please see Important Safety Information, including **Boxed Warning** below, and full Prescribing Information at www.LATUDA.com.

LATUDA received FDA approval for the treatment of adult patients with schizophrenia on October 28, 2010 and is available in the U.S. and Canada. On October 30, 2012, the FDA accepted two supplemental New Drug Applications (sNDAs) for the use of LATUDA as monotherapy and adjunctive therapy to lithium or valproate, both to treat adult patients with depressive episodes associated with bipolar I disorder (bipolar depression).

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **LATUDA is not approved for the treatment of patients with dementia-related psychosis.**

CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole)

- Concomitant use with strong CYP3A4 inducers (e.g., rifampin).

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. In short-term, placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was -0.2 ng/mL and was 0.5 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations > 5x ULN was 1.6% versus 0.6% for placebo-treated male patients.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension and in patients with known cardiovascular disease or cerebrovascular disease.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer's dementia).

Potential for Cognitive and Motor Impairment: In short-term, placebo-controlled trials, somnolence was reported in 17.0% (256/1508) of patients treated with LATUDA compared to 7.1% (50/708) of placebo patients, respectively. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Suicide: The possibility of suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Commonly Observed Adverse Reactions: (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and parkinsonism.

Before prescribing LATUDA, please read the full Prescribing Information, including **Boxed Warning** at www.LATUDA.com.

About Sunovion

About Sunovion Pharmaceuticals Inc. (Sunovion) is a leading pharmaceutical company dedicated to discovering, developing and commercializing therapeutic products that advance the science of medicine in the Psychiatry & Neurology and Respiratory disease areas and improve the lives of patients and their families. Sunovion's drug development program, together with its corporate development and licensing efforts, has yielded a portfolio of pharmaceutical products including LATUDA® (lurasidone HCl) tablets, LUNESTA® (eszopiclone) tablets, XOPENEX® (levalbuterol HCl) inhalation solution, XOPENEX HFA® (levalbuterol tartrate) inhalation aerosol, BROVANA® (arformoterol tartrate) inhalation solution, OMNARIS® (ciclesonide) nasal spray, ZETONNA® (ciclesonide) nasal aerosol and ALVESCO® (ciclesonide) inhalation aerosol.

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About Dainippon Sumitomo Pharma Co., Ltd. (DSP)

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For a copy of this release, visit Sunovion Pharmaceutical Inc.'s web site at www.sunovion.com

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[1] National Institute of Mental Health. Bipolar Disorder. [Internet] Available from: http://www.nimh.nih.gov/health/publications/bipolar-disorder/nimh-bipolar-adults.pdf. Accessed July 26, 2012.

[2] Bipolar Disorder." Decision Resources. Table 2-1: Number of Total Prevalent Cases of Bipolar Disorder in the Major Pharmaceutical Markets, by Subtype, 2008-2018. Waltham, MA. December 2009.
[3] The Depression and Bipolar Support Alliance. Mood Disorders and Different Kinds of Depression. [Internet]. Available from: http://www.dbsalliance.org/site/DocServer/DBSA_Uni_Bipolar.v3.pdf?docID=2901. Accessed March 7, 2012.
[4] *The Journal of the American Medical Association.* Bipolar Disorder Patient Page. [Internet]. Available from: http://jama.ama-assn.org/cgi/reprint/301/5/564.pdf. Accessed June 22, 2012.
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[9] National Alliance on Mental Illness. A Primer on Depressive, Bipolar and Anxiety Illnesses: Facts for Policymakers. [Internet]. Available from: http://www.nami.org. Accessed March 29, 2013 (To Access: Inform Yourself, About Public Policy, Policy Research Institute, Policymakers Toolkit).

May 20, 2013 03:10 PM Eastern Daylight Time

Sunovion Pharmaceuticals Inc. Announces Data Showing Latuda® (lurasidone HCl) was Associated with Low Rates of Weight and Metabolic Changes in Patients with Depressive Episodes Associated with Bipolar I Disorder

A Similar Pattern of Metabolic Changes was Observed in Patients Who Received LATUDA as Monotherapy or as Adjunctive Therapy to Mood Stabilizers

MARLBOROUGH, Mass.--(BUSINESS WIRE)--Sunovion Pharmaceuticals Inc. today announced it will present 18 research posters on Latuda® (lurasidone HCl), an atypical antipsychotic indicated for the treatment of adult patients with schizophrenia, at the 166th Annual Meeting of the American Psychiatric Association (APA) in San Francisco. The presentation includes results from analyses of two pivotal studies in patients with depressive episodes associated with bipolar I disorder (bipolar depression). These new data showed that LATUDA in the treatment of bipolar depression, either as monotherapy or added to ongoing treatment with lithium or valproate, was associated with low rates of change in weight, body mass index (BMI), lipid parameters and measures of glycemic control.

The two pivotal studies evaluated the efficacy and safety of LATUDA as monotherapy (PREVAIL 2) or adjunctive therapy (PREVAIL 1) for the treatment of bipolar depression, and supported two supplemental New Drug Applications (sNDAs) that were accepted by the U.S. Food and Drug Administration (FDA) on October 30, 2012.

"As such, it is critically important that we continue to evaluate the effect of LATUDA on these key measures of metabolic health, in both short and longer-term treatment."

"Sunovion is pleased to present data from two extensive research programs that studied LATUDA in patients with schizophrenia and bipolar depression," said Antony Loebel, M.D., Executive Vice President and Chief Medical Officer of Sunovion Pharmaceuticals Inc. "We are proud of the contributions we are making to improved understanding of these disorders where high unmet clinical needs remain."

Effects of LATUDA on Metabolic Indices in Bipolar Depression

The LATUDA monotherapy (PREVAIL 2) and adjunctive therapy studies (PREVAIL 1) were six-week, randomized, double-blind, placebo-controlled clinical trials that evaluated the efficacy and safety of LATUDA as monotherapy (20-60 mg/day or 80-120 mg/day vs. placebo, N=505) or adjunctive therapy (20-120 mg/day, N=348) to lithium or valproate in patients with bipolar depression, with or without rapid cycling (DSM-IV-TR). Changes from baseline to Week 6 in metabolic parameters [lipids, glucose, weight, insulin and homeostatic model assessment of insulin resistance (HOMA-IR)] were assessed [using rank ANCOVA

(LOCF) controlling for the baseline values of these metabolic parameters]. Results from the studies were as follows:

PREVAIL 2 (Monotherapy)

- Mean weight change from baseline for LATUDA vs. placebo was 0.64 vs. -0.09 lbs. (p=not significant).
- Weight gain from baseline (≥ 7%) occurred in 2.4% of patients treated with LATUDA vs. 0.7% of patients treated with placebo.
- Mean changes from baseline in metabolic laboratory parameters were: cholesterol -1.7 vs. -3.2 mg/dL, LDL -2.7 vs. -3.5 mg/dL, triglycerides 3.0 vs. 6.0 mg/dL, glucose 0.5 vs. 1.8 mg/dL, insulin 3.56 vs. 2.95 mU/L and HOMA-IR 1.08 vs. 1.19, for LATUDA vs. placebo, respectively (p=not significant for all comparisons).

PREVAIL 1 (Adjunctive Therapy)

- Mean weight change from baseline for LATUDA vs. placebo was 0.51 vs. 0.31 lbs. (p= not significant).
- Weight gain from baseline (≥ 7%) occurred in 3.1% of patients treated with LATUDA vs. 0.7% of patients treated with placebo.
- Mean changes from baseline in metabolic laboratory parameters were: cholesterol -3.0 vs. -3.8 mg/dL, LDL -3.2 vs. -2.0 mg/dL, triglycerides 9.0 vs. -6.2 mg/dL, glucose 0.9 vs. -0.3 mg/dL, insulin 1.66 vs. -0.16 mU/L and HOMA-IR 0.26 vs. -0.07, for LATUDA vs. placebo, respectively (p=not significant for all comparisons).

Using the National Cholesterol Education Program (NCEP) adult treatment panel criteria for metabolic syndrome, approximately 15% of patients met criteria for metabolic syndrome (MetS) at study baseline, which is associated with risk for diabetes and cardiovascular disease.

"Prior research has shown that patients with bipolar disorder are already at high risk for metabolic syndrome," said Loebel. "As such, it is critically important that we continue to evaluate the effect of LATUDA on these key measures of metabolic health, in both short and longer-term treatment."

In PREVAIL 1, the most frequently reported adverse events were nausea, somnolence, tremor, akathisia and insomnia. Discontinuation rates due to adverse events were 6% for LATUDA and 7.9% for placebo. In PREVAIL 2, the most frequently reported adverse events were nausea, headache, akathisia, somnolence and sedation. Discontinuation rates due to adverse events were 6% for LATUDA (either dose group) and 6% for placebo.

About Bipolar I Disorder and Bipolar Depression

Bipolar disorder, a mental illness characterized by debilitating mood swings, affects approximately 10.4 million American adults.[1,2] Bipolar depression refers to the depressive phase of bipolar disorder.[3] Symptoms of bipolar depression include: extreme sadness, anxiety, fatigue, inactivity and disinterest in usual activities, disruptions to sleeping patterns and hopelessness.[1,4] When symptomatic, most people with bipolar disorder tend to be depressed, rather than manic.[3] Bipolar disorder can also double a person's risk of early death from a range of medical conditions, including obesity, diabetes and cardiovascular disease.[5,6,7] Bipolar disorder is the sixth leading cause of disability worldwide[8] and is among the top 10 leading causes of disability in the United States (U.S.).[9]

About LATUDA

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in five six-week controlled studies of adult patients with schizophrenia. The effectiveness of LATUDA for longer-term use, that is, for more than six weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

The recommended starting dose for LATUDA for the treatment of patients with schizophrenia is 40 mg once daily taken with food (at least 350 calories) with no initial dose titration required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 160 mg/day. The maximum recommended dose is 160 mg/day. For patients with moderate and severe renal or hepatic impairment, the recommended starting dose of LATUDA is 20 mg/day. The maximum recommended dose is 80 mg/day in patients with moderate hepatic impairment and 40 mg/day in patients with severe hepatic impairment. The recommended starting dose of LATUDA in patients taking a moderate CYP3A4 inhibitor such as diltiazem is 20 mg/day with a maximum recommended dose of 80 mg/day. LATUDA should not be administered with strong CYP3A4 inhibitors such as ketoconazole or strong CYP3A4 inducers such as rifampin.

Please see Important Safety Information, including **Boxed Warning** below, and full Prescribing Information at www.LATUDA.com.

LATUDA received FDA approval for the treatment of adult patients with schizophrenia on October 28, 2010 and is available in the U.S. and Canada. On October 30, 2012, the FDA accepted two supplemental New Drug Applications (sNDAs) for the use of LATUDA as monotherapy and adjunctive therapy to lithium or valproate, both to treat adult patients with depressive episodes associated with bipolar I disorder (bipolar depression).

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **LATUDA is not approved for the treatment of patients with dementia-related psychosis.**

CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole)
- Concomitant use with strong CYP3A4 inducers (e.g., rifampin).

WARNINGS AND PRECAUTIONS

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ADVERSE REACTIONS

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Contacts

Sunovion Pharmaceuticals Inc.
Patricia Moriarty, 508-787-4279
Senior Director, Corporate Communications
patricia.moriarty@sunovion.com

DAINIPPON SUMITOMO PHARMA

Financial Results for FY2012
(The year ended March 31, 2013)

May 10, 2013

Masayo Tada, President and CEO
Dainippon Sumitomo Pharma Co., Ltd.

Sales by Product in North America and China Segments

	FY2011 Results	**FY2012 Results**	Change	FY2011 Results	**FY2012 Results**	Change
North America	(Million $)			(Billion yen)		
LATUDA®	86	**202**	116	6.9	**16.1**	9.2
LUNESTA®	528	**561**	34	42.1	**44.8**	2.7
XOPENEX®	419	**317**	- 102	33.4	**25.3**	- 8.1
BROVANA®	127	**160**	32	10.2	**12.7**	2.6
ALVESCO®	35	**38**	3	2.8	**3.1**	0.3
OMNARIS®	64	**24**	- 41	5.1	**1.9**	- 3.2
ZETONNA®	—	**5**	5	—	**0.4**	0.4
Industrial property revenues	72	**98**	26	5.8	**7.8**	2.0
Others	27	**46**	19	2.1	**3.7**	1.5
Total	1,359	**1,451**	92	108.4	**115.8**	7.4
China	(Million RMB)			(Billion yen)		
MEROPEN®	447	**494**	47	5.5	**6.3**	0.7
Others	83	**110**	27	1.0	**1.4**	0.4
Total	529	**603**	74	6.5	**7.6**	1.1

Exchange Rate:
FY2011: 1US$ = ¥79.8, 1RMB = ¥12.4
FY2012: 1US$ = ¥79.8, 1RMB = ¥12.7

Electronic Patent Application Fee Transmittal

Application Number:	11919678
Filing Date:	31-Oct-2007
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Filer:	Kendrew H. Colton/Lois Ford
Attorney Docket Number:	7379/98100

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission After Final Rejection	1809	1	840	840
		Total in USD ($)		**2240**

Electronic Acknowledgement Receipt

EFS ID:	16006881
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	42798
Filer:	Kendrew H. Colton/Lois Ford
Filer Authorized By:	Kendrew H. Colton
Attorney Docket Number:	7379/98100
Receipt Date:	11-JUN-2013
Filing Date:	31-OCT-2007
Time Stamp:	15:14:57
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2240
RAM confirmation Number	1795
Deposit Account	061135
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Extension of Time	Petition-EOT.pdf	59199 24388a06955becc9688b39ac19d6ce08b8a26fa7	no	1
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	RCE.pdf	68997 b770648ce44782ad2d1647443eb8593113dc4d23	no	2
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
3		Amendment-11June2013.pdf	1880971 4f987b93e3dfd9d388c753a60fd860f6e6bdf83c	yes	41

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Submitted/Entered with Filing of CPA/RCE	1	3
	Claims	4	10
	Applicant Arguments/Remarks Made in an Amendment	11	24
	Appendix to the Specification	25	41

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32070 b74c51b5d0aaa2a4b1d0fa9b96e8d39aef71faf5	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2041237	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/22 (03-13)
Approved for use through 3/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 7379/98100

Application Number: 11/919678

Filed: October 31, 2007

For: PHARMACEUTICAL COMPOSITION

Art Unit: 1627

Examiner: Sarah PIHONAK

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐ Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☑ Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 1400
☐ Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐ Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 061135.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration number 30,368.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Kendrew H. Colton/ — Signature

11 June 2013 — Date

Kendrew H. Colton — Typed or printed name

(202) 419-7000 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/919,678	Filing Date 10/31/2007	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 06/11/2013

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 37	Minus	** 31	= 6	X $80 =	480
Independent (37 CFR 1.16(h))	* 4	Minus	***5	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☒ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						**780**
					TOTAL ADD'L FEE	**1260**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/MOLIKI MAY/

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 06/12/2013

MMAY22 SALE #00000002 Mailroom Dt: 06/11/2013 061135 11919678
01 FC : 1801 1,200.00 DA

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 06/12/2013

MMAY22	SALE	#00000003	Mailroom Dt:	06/11/2013		061135	11919678
		01	FC : 1202	480.00	DA		
		02	FC : 1203	780.00	DA		

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 06/13/2013

MMAY22 ADJ #00000001 Mailroom Dt: 06/11/2013
Seq No: 1795 Sales Acctg Dt: 06/12/2013 061135 11919678
02 FC : 1809 840.00 CR

PATENT
Attorney Docket No. 05273.0147-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
	)
Kazuyuki FUJIHARA	) Group Art Unit: 1627
	)
Application No.: 11/919,678	) Examiner: Sarah Pihonak
	)
Filed: October 31, 2007	)
	) Confirmation No.: 6965
For: PHARMACEUTICAL COMPOSITION	)
	) **VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. § 1.114

Further to the June 11, 2013, Amendment filed in this application, Applicant submits this Supplemental Amendment Under 37 C.F.R. § 1.114 along with a Certification and Request for Prioritized Examination under 37 C.F.R. § 1.102(e).

Please amend this application as follows:

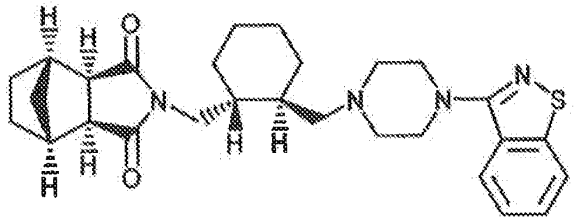
Amendments to the Claims being at page 2 of this paper.

Remarks/Arguments follow the amendment section.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

2. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising lurasidone, a pregelatinized starch and a water-soluble excipient by using a solution of a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

3. (Previously Presented) An oral preparation which is prepared by the process which comprises granulating a powder mixture comprising a pregelatinized starch and a

water-soluble excipient by a solution or dispersion of lurasidone and a water-soluble polymer binder;

wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

4. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose.

5-8. (Canceled).

9. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10. (Canceled).

11. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone in the preparation is 25 to 40% (wt/wt).

12. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. (Canceled).

16. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17-18. (Canceled)

19. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

20. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Previously Presented) The oral preparation of claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Previously presented) The oral preparation of claim 1 wherein a 50% by volume particle size of lurasidone is 0.1 to 8 μm.

23. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 25 to 40% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

25. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, a content of lurasidone in the preparation is 20 to 45% (wt/wt) and a content of lurasidone per tablet is 20 to 120 mg.

26. (Previously Presented) The oral preparation of claim 9 wherein the water-soluble excipient is mannitol or lactose.

27. (Previously Presented) The oral preparation of claim 1 wherein a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt).

28. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose.

29. (Previously Presented) The oral preparation of claim 1 wherein a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

30. (Previously Presented) The oral preparation of claim 1, further comprising a disintegrant wherein a content of the disintegrant per tablet is 0.5 to 5% (wt/wt).

31. (Previously Presented) The oral preparation of claim 1, further comprising a disintegrant wherein

a content of the disintegrant per tablet is 0.5 to 5% (wt/wt);

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation;

a content of lurasidone per tablet is 40 to 120 mg;

a pregelatinizing ratio of the pregelatinized starch is 50 to 95%;

50% by volume particle size of lurasidone is 0.1 to 8 μm;

the pregelatinized starch contains water soluble matter of 30% or less;

a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt);

the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose; and

a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

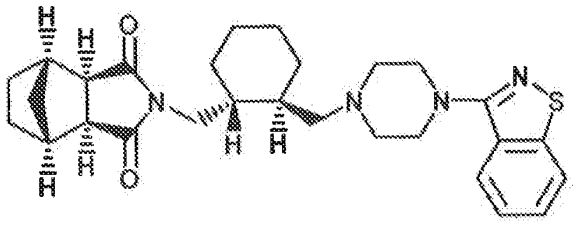
32. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 160 mg.

33. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 80 to 160 mg.

34. (Currently Amended) The oral preparation of ~~either one of claim 1 or 31~~ claim 1, wherein a similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg.

35-36. (Canceled).

37. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, wherein the oral preparation contains 20 to 45% (wt/wt) of lurasidone, the oral

preparation contains 20 mg to 120 mg of lurasidone, the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the oral preparation, and the oral preparation exhibits an equivalent dissolution profile across the range of lurasidone per oral preparation.

38. (Currently Amended) The oral preparation of ~~either one of claim 1 or 31~~ claim 1, wherein the water-soluble excipient is one or more selected from the group consisting of mannitol, lactose, saccharose, sorbitol, D-sorbitol, erythritol and xylitol.

39. (Currently Amended) The oral preparation of ~~either one of claim 30 or 31~~ claim 30, wherein the disintegrant is one or more selected from the group consisting of corn starch, crystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium and crospovidone.

REMARKS

Following entry of the Amendment, claims 1-4, 9, 11-14, 16, 19-34, and 37-39 (4 independent claims and 29 total claims) will be pending. The claims have been amended to remove all multiple dependencies. Specifically, claims 34 and 38 have been amended to depend from claim 1 and claim 39 has been amended to depend from claim 30. In addition, claims 5-7, 35, and 36, which are withdrawn by the Office as being directed to a non-elected invention, are cancelled without prejudice or disclaimer. The specification provides written description support for the amended claims. Accordingly, no new matter is added by the amendments provided herein. Their entry is respectfully requested.

If there is any fee due in connection with the filing of this Supplemental Amendment, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 6, 2013

By: Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266
(202) 408-4000

PATENT
Attorney Docket No. 05273._____-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
	)
Kazuyuki FUJIHARA	) Group Art Unit: 1627
	)
Application No.: 11/919,678	) Examiner: Sarah Pihonak
	)
Filed: October 31, 2007	)
	) Confirmation No.: 6965
For: PHARMACEUTICAL COMPOSITION	)
	) VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

REVOCATION OF POWER OF ATTORNEY
STATEMENT UNDER 37 C.F.R. § 3.73(b)
AND GRANT OF NEW POWER OF ATTORNEY

The undersigned, a representative authorized to sign on behalf of the assignee owning all of the interest in this patent application, hereby revokes all previous powers of attorney or authorization of agent granted in this application before the date of execution hereof.

As required by 37 C.F.R. § 3.73(b), the undersigned verifies that DAINIPPON SUMITOMO PHARMA CO., LTD., is the assignee of the entire right, title, and interest in the patent application identified above by virtue of an assignment from the inventor recorded in the U.S. Patent and Trademark Office (USPTO) at Reel 020124, Frame 0821. A corrective assignment was recorded in the USPTO at Reel 021008, Frame 0209, to correct the address of the assignee.

The undersigned representative of the Assignee hereby grants its power of attorney to the patent practitioners associated with **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Customer No. 22,852**, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and to receive the Letters Patent.

Please send all future correspondence concerning this application to Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., Customer No. 22,852.

Dated: December 4, 2013

By:_____
Masayo TADA
Representative Director, President and
Chief Executive Officer of Dainippon
Sumitomo Pharma Co., Ltd.

Electronic Patent Application Fee Transmittal

Application Number:	11919678
Filing Date:	31-Oct-2007
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Filer:	Charles E. Van Horn/Charlene Woods
Attorney Docket Number:	7379/98100

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**4140**

Electronic Acknowledgement Receipt

EFS ID:	17593939
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	42798
Filer:	Charles E. Van Horn/Charlene Woods
Filer Authorized By:	Charles E. Van Horn
Attorney Docket Number:	7379/98100
Receipt Date:	06-DEC-2013
Filing Date:	31-OCT-2007
Time Stamp:	17:46:28
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$4140
RAM confirmation Number	5259
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	TrackOne Request	Certification_and_Request_for_Prioritized_Exam.pdf	86388 919cb7dafc620e97a4204b960f7d22a648fa3942	no	1
Warnings:					
Information:					
2		Supplemental_Amendment.pdf	337905 2534e6313ef538e48c07acb5dd914b25d35514d9	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	7
	Applicant Arguments/Remarks Made in an Amendment	8	8

Warnings:					
Information:					
3	Power of Attorney	Revocation_of_POA-Grant_of_New_POA.pdf	76597 72adaac9fd396f60147b9d474cdf648df05a4e76	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32173 320c2791ec37f179ea0d270e030c242de95193eb	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	533063	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e)

First Named Inventor	Kazuyuki FUJIHARA	Nonprovisional Application Number (if known):	11/919,678
Title of Invention	PHARMACEUTICAL COMPOSITION		
Attorney Docket Number	05273.0147-00		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUEST PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application

II. ☒ Request for Continued Examination - Prioritized Examination under 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.

ii. If the application is a utility application, this certification and request is being filed via EFS-Web.

iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.

iv. This certification and request is being filed prior to the mailing of a first Office Action responsive to the request for continued examination.

v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

The Commissioner is hereby authorized to charge any additional filing fees, including any fees necessary to complete the Track 1 requirements, to Deposit Account No. 06-0916.

Charles E. Van Horn

Charles E. Van Horn
Reg. No.: 40,266
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
202-408-4000

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/919,678	Filing Date 10/31/2007	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/06/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 29	Minus	** 37	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***5	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/TAMMY L. ACREE/

Document code: WFEE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/919,678	10/31/2007	Kazuyuki Fujihara	05273-00

CONFIRMATION NO. 6965

22852
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

POA ACCEPTANCE LETTER

OC000000065445866

Date Mailed: 12/19/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/06/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/afessehaye/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/919,678	10/31/2007	Kazuyuki Fujihara	7379/98100

CONFIRMATION NO. 6965

42798
FITCH, EVEN, TABIN & FLANNERY, LLP
One Lafayette Center
1120 20th Street, NW, Suite 750 South
WASHINGTON, DC 20036

POWER OF ATTORNEY NOTICE

OC000000065445847

Date Mailed: 12/19/2013

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/06/2013.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/afessehaye/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON DC 20001-4413

MAILED
DEC 30 2013
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 11/919,678

1. THE REQUEST FILED December 6, 2013 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at 571-272-4584. In his/her absence, calls may be directed to Brian Brown, 571-272-5338.

/JoAnne Burke/
[Signature]

Paralegal Specialist, Office of Petitions
(Title)

PATENT
Attorney Docket No. 05273.0147-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Kazuyuki FUJIHARA	)	Group Art Unit: 1627
	)	
Application No.: 11/919,678	)	Examiner: Sarah Pihonak
	)	
Filed: October 31, 2007	)	
	)	Confirmation No.: 6965
For: PHARMACEUTICAL COMPOSITION	)	
	)	VIA EFS-WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

SECOND SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. § 1.114

Further to the December 6, 2013, Supplemental Amendment filed in this application, Applicant submits this Second Supplemental Amendment under 37 C.F.R. § 1.114.

Please amend this application as follows:

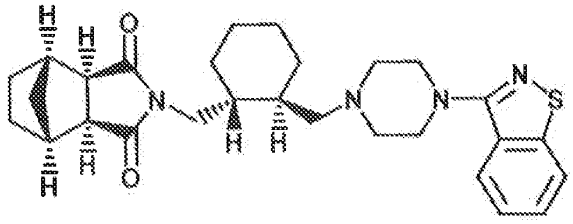
Amendments to the Claims being at page 2 of this paper.

Remarks/Arguments follow the amendment section.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the preparation.

2. (Canceled).

3. (Canceled).

4. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose.

5-8. (Canceled).

9. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10-11. (Canceled).

12. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. (Canceled).

16. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17-19. (Canceled).

20. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Previously Presented) The oral preparation of claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Previously presented) The oral preparation of claim 1 wherein a 50% by volume particle size of lurasidone is 0.1 to 8 μm.

23. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Canceled).

25. (Currently Amended) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, ~~a content of lurasidone in the preparation is 20 to 45% (wt/wt)~~ and a content of lurasidone per tablet is 20 to 120 mg.

26. (Previously Presented) The oral preparation of claim 9 wherein the water-soluble excipient is mannitol or lactose.

27. (Previously Presented) The oral preparation of claim 1 wherein a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt).

28. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose.

29. (Previously Presented) The oral preparation of claim 1 wherein a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

30. (Previously Presented) The oral preparation of claim 1, further comprising a disintegrant wherein a content of the disintegrant per tablet is 0.5 to 5% (wt/wt).

31. (Currently Amended) The oral preparation of claim 1, further comprising a disintegrant wherein

a content of the disintegrant per tablet is 0.5 to 5% (wt/wt);

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation;

a content of lurasidone per tablet is 40 to 120 mg;

a pregelatinizing ratio of the pregelatinized starch is 50 to 95%;

50% by volume particle size of lurasidone is 0.1 to 8 μm;

the pregelatinized starch contains water soluble matter of 30% or less;

the water-soluble excipient is mannitol or lactose, and a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt);

the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose; and

a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

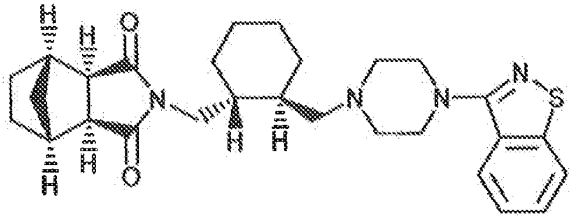
32. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 160 mg.

33. (Canceled).

34. (Previously Presented) The oral preparation of claim 1, wherein a similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg.

35-36. (Canceled).

37. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, wherein the oral preparation contains 20 to 45% (wt/wt) of lurasidone, the oral

preparation contains 20 mg to 120 mg of lurasidone, the pregelatinized starch is incorporated in an amount of 10 to 50% (wt/wt) based on the weight of the oral preparation, and the oral preparation exhibits an equivalent dissolution profile across the range of lurasidone per oral preparation.

38. (Currently Amended) The oral preparation of claim 1, wherein the water-soluble excipient is one or more selected from the group ~~consisting~~ of mannitol, lactose, saccharose, sorbitol, D-sorbitol, erythritol and xylitol.

39. (Currently Amended) The oral preparation of claim 30, wherein the disintegrant is one or more selected from the group ~~consisting~~ of com starch, crystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium and crospovidone.

40. (New) The oral preparation of claim 1, further comprising a lubricant, wherein a content of the lubricant per tablet is 1.0% (wt/wt) to 1.43% (wt/wt).

41. (New) The oral preparation of claim 40, wherein the lubricant is selected from the group of magnesium stearate, talc, polyethylene glycol, silica and hydrogenated vegetable oil.

42. (New) The oral preparation of claim 1, wherein the oral preparation is a tablet.

43. (New) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone), a pregelatinized starch,

a water-soluble excipient and a water-soluble polymer binder, wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt),

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation,

the water-soluble excipient is mannitol or lactose, and

the water-soluble polymer binder is one or more agents selected from the group of hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and polyvinyl alcohol.

44. (New) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone), a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, and further comprises a disintegrant and a lubricant, wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt),

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation,

the water-soluble excipient is mannitol,

the water-soluble polymer binder is hydroxypropylmethylcellulose, and

the oral preparation is a tablet.

45. (New) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 50% (wt/wt) based on the weight of the preparation.

REMARKS

I. Status of Claims

Following entry of the Amendment, claims 1, 4, 9, 12-14, 16, 20-23, 25-32, 34, and 37-45 (4 independent claims and 29 total claims) will be pending. Claims 25, 31, 38, and 39 are amended, claims 2, 3, 11, 19, 24, and 33 are canceled, and claims 40-45 are added herein. The specification, *e.g.*, ¶¶[0022], [0023], [0044], [0047], and [0149] (formulations RP-03320 and RP-03322) of U.S. Patent Application Publication No. 2009/0143404 A1 ("the '404 publication"), which is the publication of the present application, and original claim 9, provide written description support for the amended claims. Specifically, the lower limit, i.e. 1.0%, of new claim 40 is calculated from formulation RP-03322 in Table 36 in paragraph [0149] of the '404 publication, where the formulation contains 2 mg of magnesium stearate and the total amount of the formulation is 200 mg (2 mg/200 mg x 100 = 1.0%); similarly, the upper limit, i.e. 1.43% of new claim 40, is calculated from formulation RP-03320 in Table 36 in paragraph [0149] of the '404 publication, where the formulation contains 4 mg of magnesium stearate and the total amount of the formulation is 280 mg (4 mg/280 mg x 100 = 1.43%). Accordingly, no new matter is added by the amendments provided herein. Entry of the amendments is respectfully requested.

II. Rejection over EP Patent Publication No. 1 327 440 A1 to Fujihara et al. ("Fujihara") in view of U.S. Patent No. 4,600,579 to Salpekar et al. ("Salpekar")

Claims 1-4, 9, 11-14, 16, 19-34, and 37 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Fujihara in view of Salpekar. Final Office Action dated

December 11, 2012, at p. 10. Applicant traverses the rejection for at least the following reasons.

A. Claims 1, 4, 12-14, 16, 21-23, 26-30, 32, 34, and 37-42 (claims 2, 3, 11, 19, 24, and 33 have been canceled)

As previously pointed out, the characteristics of the present invention include:

> 1) the oral preparation of the present invention includes a high lurasidone content per tablet, particularly high content ratio (%) of 20 to 45% (wt/wt) of lurasidone as recited in claims 1 and 37 - which allows for the employment of relatively high total amounts of lurasidone in a relatively small sized tablet, while, at the same time, the oral preparation exhibits beneficial dissolution properties (*see, e.g.*, paragraph [0149] of the '404 publication).
>
> 2) the oral preparation of the present invention incorporates pregelatinized starch in a range of 10 to 50% (wt/wt) based on the weight of the preparation; and
>
> 3) the preparation of the present invention has beneficial dissolution properties; that is, the preparation shows equivalent dissolution profiles as between oral preparations having different contents of lurasidone, as reflected by a similarity factor (f2) of $50 \leq f2 \leq 100$[1], and furthermore exhibits rapid dissolution (*e.g.*, a dissolution of at least 85% of the initially present lurasidone within 30 minutes).

Neither Fujihara or Salpekar teach or suggest the claimed oral preparation or its advantages.

1. Fujihara teaches away from higher amounts of lurasidone in an oral preparation.

The Fujihara preparations with a low content of luradisone (*e.g.*, the film-coated formulations disclosed in Table 28 at ¶ [0128] of the '404 publication, which contain

[1] Dependent claim 34 is directed to an oral preparation according to claim 1, wherein the similarity factor f2 of each preparation is in the range of $50 \leq f2 \leq 100$ when a content of lurasidone per tablet changes over a range of 20 to 120 mg. Neither Fujihara or Salpekar teaches or suggests claim 34.

12.2% and 12.3% of lurasidone in the film-coated tablets[2]) show similar dissolution profiles (f2-value of 77) and rapid dissolution (30-minute dissolution ratio values of 91% and 92%, respectively). *See* the '404 publication at Figure 1 and Tables 26-28 at ¶¶ [0126]-[0128] of the specification (Patent Document 2 is identified as WO 2002/024166 (Fujihara) at ¶ [0008] of the '404 publication). Fujihara, however, teaches that tablets comprising 16.3% (wt/wt) or more of lurasidone have inferior dissolution profiles as compared with tablets comprising lesser amounts of lurasidone. This is seen from the tablets prepared in Comparative Examples 1-3 in Fujihara, which include tablets comprising 16.3% (wt/wt), 17.1% (wt/wt), 29.0% (wt/wt) of lurasidone, respectively.[3] *See* Fujihara at pages 27-30, paragraphs [0180] to [198]. According to Fujihara, the tablets of Comparative Examples 1-3 are **significantly inferior** in terms of the dissolution characteristics to the corresponding tablets of Examples 2-28 which comprise 8.13-16.3% (wt/wt) of lurasidone (*see* ¶¶ [0185], [0191], [0197] and [0198]). Specifically, Fujihara teaches that the dissolution percentage of tablet in Comparative Example 3 was merely 74% at 15 minutes, and only 84% after 30 minutes, while the dissolution percentage for the tablets of Examples 20-28 was over 84% at 15 minutes and in almost all instances over 90% after 30 minutes (Ex. No. 23 has a dissolution of

[2] The percent of lurasidone in each of the film-coated tablets in Table 28 was calculated by dividing the amount of lurasidone in each tablet (10 mg and 40 mg, respectively) by the total weight of the film-coated formulation (82.006 mg and 324.01 mg, respectively). For example, 10 mg/82.006 mg x 100 = 12.2% and 40 mg/324.01 mg x 100 = 12.3%.

[3] The percent of lurasidone in each of the film-coated tablets in Comparative Examples 1-3 in Fujihara was calculated by dividing the amount of lurasidone in each tablet (20 mg, 20 mg, and 40 mg, respectively) by the total weight of the film-coated formulation (123 mg, 117 mg, and 137.7 mg, respectively). For example, 20 mg/123 mg x 100 = 16.3%, 20 mg/117 mg x 100 = 17.1% and 40 mg/137.7 mg x 100 = 29.0%. Applicants note that Table 42 indicates that the content of the uncoated tablet of (a) is 120 mg, but the sum of the content of the ingredients of the uncoated tablet listed in Table 41 is actually 114 mg, not 120 mg.

87% at 30 min.). *See id.* at ¶ [0197].[4] Similarly, data provided in Test 1 (Tables 1-5, Figure 2 and Comparative Examples 1 and 2) of Applicant's specification also supports Fujihara's proposition that tablets comprising 16.3% (wt/wt) or more of lurasidone have inferior dissolution profiles as compared with tablets comprising lesser amounts of lurasidone.

In Comparative Examples 1 and 2 of Test 1, two tablets comprising 40 mg (12.3% (wt/wt)), and 80 mg, (24.7% (wt/wt)) respectively, of lurasidone per tablet were manufactured on the basis of the formulation disclosed in Fujihara. *See* ¶¶ [0089]-[0098] of the '404 publication.[5] According to Test 1, Fujihara's tablet comprising 24.7% (wt/wt) of lurasidone (80 mg tablet, Comparative Example No. 2) clearly shows a lower dissolution profile than a tablet comprising 12.3% (wt/wt) of lurasidone (40 mg tablet, Comparative Example No. 1). *See* Applicant's specification at Figure 2. Based on these teachings in Fujihara, one of ordinary skill in the art would have focused on preparing tablets with 8.13-16.3% (wt/wt) of lurasidone as in Fujihara's Examples 2-28, and would have been led away from preparing oral preparations with higher amounts of

[4] The U.S. FDA reference document, "Guidance for Industry," which was submitted with the Amendment filed September 13, 2012, explains that "an IR [i.e., immediate release] drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes (…)."

[5] The percent of lurasidone in Comparative Examples 1 and 2 in Test 1 was calculated by dividing the content of lurasidone in each formulation by the total amount of the film-coated tablet formulation. For example, the percentage of lurasidone in Comparative Example 1 was calculated by dividing 40 mg, the amount of lurasidone in Comparative Example 1, by the total weight of the film-coated formulation provided in Table 3 in paragraph [0094] of the '404 publication (40 mg/324.01 mg x 100 = 12.3%); similarly, the percent of lurasidone in Comparative Example 2 was calculated by dividing 80 mg, the amount of lurasidone in Comparative Example 2, by the total weight of the film-coated formulation provided in Table 3 of paragraph [0094] of the '404 publication (80 mg/324.01 mg x 100 = 24.7%).

lurasidone, *e.g.*, 20 to 45% (wt/wt), as in claims 1, 4, 9, 12-14, 16, 21-23, 26-30, 32, 34, and 37-42 of the present application.

2. Oral preparations comprising PGS in accordance with the present claims are unexpectedly superior as compared with oral preparations without PGS and would not be predicted based on the teachings of the prior art.

The data shown in Table 3 below compares a preparation of Example 4 of Applicant's specification to a Comparative formulation prepared in the same manner as Example 4 except that 0 (zero) percent (%) of pregelatinized starch was used and the amount of sodium croscarmellose was increased.

Table 3

Components	Example 4 of the original specification		Comparative formulation	
	mg	wt/wt%	mg	wt/wt%
Lurasidone	80	25	80	25
Mannitol	176	55	176	55
PGS (pregelatinized starch)	40	**12.5**	0	**0**
Ac-Di-Sol **(Croscarmellose Na)**	8	**2.5**	48	**15**
HPMC (Hypromellose, **Hydroxypropyl methylcellulose)**	12	3.75	12	3.75
Magnesium stearate	4	1.25	4	1.25
Total	320	100	320	100
30-minute dissolution values	*86%*		*70%*	

As can be seen from Table 3, the 30-minute dissolution value for the tablet according to the claimed invention is 86%. This is significantly better than the value of

70% which is achieved by the Comparative formulation which does not contain pregelatinized starch.[6] Applicant respectfully submits that the evidence in Table 3 above shows that the claimed oral preparation has superior dissolution values as compared with the Comparative formulation. These results would not be expected by one of ordinary skill in the art or predicted from the teachings of the prior art including Fujihara and Salpekar.

While Applicant does not concede that the Office has established a *prima facie* case of obviousness based on the cited references, Applicant submits that the evidence in Table 3 above is sufficient to rebut any *prima facie* case of obviousness that has been established.

3. One of ordinary skill in the art would not be able to predict the results obtained with a highly water insoluble ingredient such as lurasidone based on the teachings of Salpekar.

Salpekar discloses that "PGS is included in an amount effective for imparting to the composition the capability of being formed into tablets having high hardness . . ., short disintegration time (e.g., about 10 minutes or less), and short dissolution time (e.g., about 20 minutes or less for 80% or more of the APAP to dissolve)". Salpekar at col. 4, lines 3-9. Salpekar does not provide any data showing that adding PGS to a composition shortens dissolution times. On the contrary, as shown in Examples 1-3 of Salpekar, increasing PGS (Ex. 2 (8.85% PGS) vs. Ex. 1 (18.0% PGS)) actually

[6] As the Office will notice, the Comparative formulation in Table 3 above includes 48 mg of Croscarmellose Na, which is six times the amount of Croscarmellose Na in Example 4 of the original specification. But, this would not alter the conclusion drawn from the comparison provided in Table 3. Croscarmellose Na is a typical disintegrant and one of ordinary skill in the art would expect Croscarmellose Na to increase dissolution values (or shorten dissolution times); however, as shown in Table 3, the dissolution value of Comparative formulation is lower (or the dissolution time is more prolonged) than Example 4 in the original specification.

prolonged rather than shortened the disintegration time of the compositions. Moreover, there was no need to improve dissolution in Salpekar because the active ingredient being used therein, N-acetyl-p-aminophenol (also referred to as APAP or acetaminophen), is already highly water soluble.

The compositions disclosed in Salpekar exclusively focus on water soluble acetaminophen.[7] In contrast, lurasidone is water insoluble.[8] There is no reason based on the teachings of Salpekar that a person of ordinary skill in the art would have been directed towards using PGS with a water insoluble ingredient such as lurasidone. Further, one of ordinary skill in the art could not predict or expect the superior dissolution values achieved when combining lurasidone and PGS. PGS is known to be a binder and improve tablet crushing strength, and binder effectiveness is known to be related to optimization of tablet properties, especially crushing strength, which is the most strongly affected tablet property. *See* Becker et al., "Effectiveness of Binders in Wet Granulation: A Comparison Using Model Formulations of Different Tabletability," Drug Development and Industrial Pharmacy, 23(8), pp. 791-808 ("Becker"), p. 791, abstract at lines 1-3 ("Based on an analysis of model granulates and tablets, a comparison was made of the binders, . . . Lycatab PGS, ... "), and p. 806, left-column at lines 16-17 ("The main effect of Lycatab PGS [a pregelatinized maize starch] is the improvement of tablet crushing strength."); *see also* Becker at p. 802, right-column at lines 11-17 ("Binder effectiveness refers to the degree to which the lowest possible

[7] Acetaminophen has an experimental water solubility of 14 mg/mL. *See* DrugBank (http://www.drugbank.ca/drugs/DB00316, previously submitted.
8 Lurasidone has a water solubility of 0.224 mg/ml at 20°C, which is more than an order of magnitude less than that for acetaminophen.

concentration of a binder can contribute to the optimization of *all* granulate and tablet properties. . . . The tablet property most strongly affected is crushing strength.") Since a PGS formulation was demonstrated to improve tablet crushing strength, and thus shown to act as an effective binder, one of skill in the art would not expect the addition of PGS to a composition to shorten (improve) the dissolution time but rather would expect to actually prolong or lengthen the dissolution time; however, as shown in Table 3 above, the testing comparing the claimed oral preparation (comprising, *inter alia*, lurasidone and PGS) to the closest prior art, a comparative formulation (comprising, *inter alia*, lurasidone and no PGS) showed that the claimed preparation outperformed the Comparative formulation by a substantial margin. These results would not be expected by one of ordinary skill in the art or predicted from the teachings of the prior art including Fujihara and Salpekar.

B. Claims 9, 20, 25, 31, and 43-45

1. Fujihara and Salpekar fail to teach or suggest the amount of pregelatinized starch recited in claims 9, 20, 25, 31, and 43-45.

New independent claims 43 and 44 are directed to oral preparations comprising, *inter alia*, pregelatinized starch in an amount of 20 to 30% (wt/wt) based on the weight of the preparation. Dependent claims 9, 20, 25, and 31 also recite that the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation. New dependent claim 45 is directed to an oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 50% (wt/wt) based on the weight of the preparation. Fujihara is completely silent regarding the use of pregelatinized starch, which the Office acknowledges on page 12 of the Final

Office Action dated December 11, 2012. The Office relies on Salpekar to cure this deficiency in Fujihara.

As mentioned above, Salpekar is directed to compositions comprising acetaminophen. *See* Salpekar at col. 1, lines 6-10. Salpekar teaches that "PGS is included in an amount effective for imparting to the composition the capability of being formed into tablets having high hardness . . ., short disintegration time . . . and short dissolution time . . . ." *See id.* at col. 4, lines 3-9. Specifically, Salpekar teaches that an effective amount of PGS is from about 5 or less to about 15 or more parts per 100 parts of the composition or about 5% to about 15% PGS. *See id.* at col. 4, lines 15-17. The range of PGS disclosed in Salpekar is clearly outside the range of 20 to 30% (wt/wt) as recited in new independent claims 43 and 44 and dependent claims 9, 20, 25, and 31, and is also clearly outside the range of 20 to 50% (wt/wt) as recited in new dependent claim 45. Further, there is nothing in Salpekar or Fujihara that would teach or suggest using higher amounts of PGS. In fact, Salpekar teaches away from using more than 15% (wt/wt) of PGS in its compositions.

Examples 1-3 in Salpekar provide a comparison of three compositions with differing amounts of PGS, an auxiliary binder, and an auxiliary disintegrating agent. *See* Salpekar at col. 8, lines 17-50. Example 1 in Salpekar includes 18.0 % of PGS, Example 2 includes 8.85% of PGS and 1.0% of PVP (aux. binder). The disintegration time of Example 1 is 18 minutes, which is 300% longer than the disintegration time for the composition of Composition 2 (6 minutes). The poorer disintegration results reported with Example 1, which includes 18% pregelatinized starch, would have led away from using 20 to 30% (wt/wt) of PGS as recited in independent claims 43 and 44

and dependent claims 9, 20, 25, and 31 or higher amounts of PGS such as 20 to 50% (wt/wt) of PGS as recited in dependent claim 45. Indeed, based on the Examples in Salpekar, increasing the amount of PGS would have suggested longer, not shorter disintegration times in an acetaminophen tablet, and longer disintegration times would have been contrary to Salpekar's stated objective. *See* Salpekar at col. 4, lines 3-9 (PGS is included in an amount effective for imparting a composition the capability of being formed into tablets having high hardness (e.g., about 8 kp or more), [and] short disintegration time (e.g., about 10 minutes or less) . . . .).

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI). Indeed, the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is "strong evidence of unobviousness." *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986). When the disclosure of Salpekar is considered in its entirety, as required, *see* M.P.E.P. § 2141.02(VI), a person would have been directed away from using higher amounts of PGS such as 20 to 30% (wt/wt) or 50% (wt/wt) of PGS. For at least this reason, Applicant submits that independent claims 43 and 44 and dependent claims 9, 20, 25, 31, and 45 would not have been obvious over Fujihara and Salpekar.

Applicants appreciate that Example 2 includes an auxiliary binder, PVP, in addition to PGS, but Applicant submits that PVP is known to delay (lengthen) rather than shorten disintegration. *See* Becker at p. 802, right-column at lines 4-6 (1997). Thus, the shortened disintegration time observed in Example 2 in Salpekar is a result of the reduced amount of PGS, not the inclusion of PVP.

For at least the foregoing reasons, Applicant respectfully requests that the Office reconsider and withdraw the rejection.

III. Rejection over claims of co-pending U.S. Application No. 12/997,779

Claims 1-4, 9, 11-14, 16, 19-34, and 37 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1-7 of co-pending U.S. Application No. 12/997,779. Office Action at p. 16.

A proper rejection under the doctrine of non-statutory obviousness-type double patenting requires an analysis that "parallels the guidelines for a 35 U.S.C. 103(a) rejection," see M.P.E.P. § 804(II)(B)(1), including for example, ascertaining "the differences between the claimed invention and the prior art." *See* M.P.E.P. § 2141(II).

Claims 1-7 of U.S. Application No. 12/997,779 ("the '779 application") have been amended to recite a tablet comprising, *inter alia*, an active ingredient selected from a group of droxidopa, levodopa, ethenzamide, ibuprofen, indomethacin, amoxicillin, cephalexin, erythromycin and clarithromycin. Lurasidone, the active ingredient recited in present claims 1, 4, 9, 12-14, 16, 20-23, 25-32, 34, and 37-45, is not listed as an active ingredient in the claims of the '779 application. Thus, claims 1-7 of the '779 application fail to teach or suggest every element of present claims 1, 4, 9, 12-14, 16, 20-23, 25-32, 34, and 37-45. For at least this reason, the provisional rejection of claims 1, 4, 9, 12-14, 16, 20-23, 25-32, 34, and 37 under the doctrine of non-statutory obviousness-type double patenting should be withdrawn, and Applicants respectfully request withdrawal of the same.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

If there is any fee due in connection with the filing of this Supplemental Amendment, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266
(202) 408-4000

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RESEARCH PAPER

Effectiveness of Binders in Wet Granulation: A Comparison Using Model Formulations of Different Tabletability

D. Becker,[1] T. Rigassi,[1] and A. Bauer-Brandl[2]

[1]*Novartis, Inc., Building K-401.2.65, CH-4002 Basel, Switzerland*
[2]*Universität Freiburg, Pharmazeutische Technologie, Hermann-Herder-Str. 9, D-79104 Freiburg, Germany*

ABSTRACT

Based on an analysis of model granulates and tablets, a comparison was made of the effectiveness of the binders PVP K30 PH, Cellulose HP-M 603, Lycatab DSH, Lycatab PGS, and L-HPC (type LH 11). A high shear mixer was used to prepare two model granulates (placebo and paracetamol) under processing conditions which were, as far as possible, comparable. The binders were added as proportions of 2%, 6%, and 10%. Water was used as the granulating liquid. The properties of the placebo granulates (particle size distribution, bulk and tapped density, granule strength, flow properties), and those of the tablets (crushing strength, friability) prepared from these granulates under different compaction forces, were generally good. However, with PVP, Cellulose HP-M603, and Lycatab, the disintegration time of the tablets did not meet pharmacopoeial requirements even though a "disintegrant" was used in the "outer phase." The paracetamol formulations were prime examples of high-dose drug substances with particularly poor granulating and tabletting properties, well suited to reveal differences between the binders. The paracetamol granulates were of higher friability and less flowability than the placebo granulates. The tablets tended to cap, friability was (with few exceptions) high, and disintegration times were long. In the preparation of model tablets containing paracetamol, PVP K30 PH (6%), and Cellulose HP-M 603 (6%) turn out to be the binders of choice with respect to crushing strength, but the disintegration times are too long. Lycatab PGS, Lycatab DSH, and L-HPC-LH 11 could not be used to produce paracetamol tablets that met the requirements.

An assessment method involving calculation of averages for all granulates is used to evaluate the effectiveness of the binders.
***Key Words:** Wet granulation; High shear mixer; Binder; Tablet; Hydroxypropylmethylcellulose; Polyvinylpyrrolidone; Lycatab; L-HPC.*

INTRODUCTION

The properties of wet granulates, and of the tablets into which they are processed, are decisively influenced by binders. Not only are the type and amount of binder important, but also the processing procedure, e.g. the initial and then thorough wetting of the tablet mass (1). A standard method for wet granulation in a high shear mixer involves the dry addition of binder, followed by mixing, and then the addition of water. In this method a good correlation was found between granulate particle size and binder concentration (2), and in addition, this method does not require the preparation of a binder solvent.

The aim of the present study is to compare the effectiveness of different binders when used for wet granulation in a high shear mixer.

Commercial formulations of the binders polyvinylpyrrolidone (PVP K30 PH) and hydroxypropylmethylcellulose (Cellulose HP-M 603) are widely used (3) and serve here as a reference. Lycatab PGS™ (a pregelatinised maize starch), Lycatab DSH™ (a maltodextrin), and L-HPC, type LH 11™ (a low-substituted hydroxypropylcellulose) are used less frequently or are new.

Two models, a placebo formulation and a drug formulation, were assessed. The latter was given a very high content of paracetamol so that its tableting properties would be particularly unfavorable. The influence of different types and amounts of binders both on granulate properties (particle size distribution, bulk, and tapped density, granule strength, flow properties) and on tablet quality (crushing strength, friability, disintegration time) was investigated.

The degree to which wetting affects the particle size of the agglomerates depends to a large extent on the adhesion properties between binder and powder (4,5). Powder wettability is particularly important for binder distribution in the granules (6) and for the mechanical properties of the tablets (7). For this reason, it was not possible in the present study to go to the literature for data on the reference substances. However, since particle enlargement is for the most part unrelated to the the particular machines used (4,8), these observations can be applied to other manufacturing situations.

MATERIALS AND METHODS

Preparation of the Granulates

The raw materials used in the preparation of the granulates are listed in Table 1. Of the 1800 g in each granulate, 89.3% of the final mixture was the "inner" phase and 10.7% was the "outer" phase. Table 2 summarizes the compositions of the formulations.

The manufacturing steps for the granulates are listed in Table 3.

Properties of the Granulates

Particle size distribution of the granulates was determined twice in each case, on 50 g portions of granulate, using a laboratory VE 1000/s sieving machine (Kurt Retsch GmbH & Co. KG, 42781 Haan, Germany) set to run for 10 minutes at an amplitude of 1.5 mm. The stack consisted of analytical-grade screens conforming to DIN/ISO 3310/1, with mesh sizes of 1000, 710, 630, 500, 315, 250, 200, and 100 μm.

The *bulk and tapped density* of the granulates were assessed in accordance with the Germany pharmacopoeia (DAB 1966) using a JEL tamped volume measuring apparatus (STAV 2003, J. Engelsmann AG, 6700 Ludwigshafen, Germany). V_{250} is the result reported.

The *granule strength* was determined by testing friability using the "Roche" oscillating friability testing machine. The testing drum, equipped with two steel rollers, alternately rolls 50 times to the left and right, rotating 170° each time. 10 g of granulate from the 250–800 μm sieve fraction was used for the test of granule strength. After the drum movement stopped, the granulate was sieved for 2 min through a 250 μm sieve, with an air throughput of (48–58) m^3/hr, using the Alpine 200 LS air-jet sieving machine (Alpine AG, 8900 Augsburg, Germany), and the residue remaining on the sieve was weighed. The granule strength was calculated using the following formula:

Table 1

Materials

Name	Manufacturer	Batch
Lycatab PGS	Roquette Fréres, F-Lille	E8213
Lycatab DSH	Roquette Fréres, F-Lille	E5810
L-HPC Typ: LH-11	ShinEtsu Chemicals, J-Tokio	501019
Cellulose HP-M 603	DOW Chemical USA, Midland, MI, USA	JJ15012N23
PVP K 30 PH	I.S.P., Guildford, U.K.	TX51028
Lactose, ground	De Melkindustrie Holland, NL-Veghel	024448
Avicel PH 102	FMC, Philadelphia, PA, USA	Y541
PVP XL	I.S.P., Guildford, U.K.	S50529
Aerosil 200	CABOT Corp., Tuscola, IL, USA	
Magnesium stearate	FACI Italien ??	MGS-30159
Paracetamol	Hou Zhou Syn. Pharm. Fact.	9512082(M) 9512105

$$\text{granule strength} = \frac{\text{final weight of sieve residue} * 100}{\text{weight of sample}}$$

The *flow properties* of the granulates were assessed using a Flowtester FT 300 from Sotax (Sotax AG, 4123 Allschwil, Switzerland). A single sample of 350 g of granulate was used for each of the 6 measurements (with differing funnel vibrations). The flow angle quotient is reported in each case as the result. According to Sotax (9), values in excess of 0.8 indicate that flow is good, while those below 0.6 indicate that it is poor.

Pressing Into Tablets

An EKO laboratory model eccentric tablet press (Emil Korsch, Berlin, Germany) was used to press 400 mg tablets, 10 mm in diameter and with bevelled edges, at a rate of 52 tablets per min.

The compaction forces and tolerances used in the preparation of batches of 100 tablets were: (5.0 ± 0.25) kN, (7.5 ± 0.35) kN, (10.0 ± 0.50) kN, (12.5 ± 0.60) kN, (15.0 ± 0.75) kN, (17.5 ± 0.90) kN, (20.0 ± 1.20) kN, (25.0 ± 1.80) kN, and (35.0 ± 2.00) kN.

Tablet Properties

Tablet friability was determined by placing 20 tablets each time into a "Roche" friability testing machine and then setting the machine for 500 revolutions. The friability of the tablets was calculated using the following formula:

Table 2

Composition of Finished Blends

		Placebo	Paracetamol
	Material	Proportion [M/M]	Proportion [M/M]
Inner phase	1 paracetamol	0%	75%
	2 lactose/Avicel 2.45 : 1	ad 100%	ad 100%
	4 binder	0%, 2.0%, 6.0%, 10%	0%, 2.0%, 6.0%, 10%
Outer phase	6 Avicel	5.0%	5.0%
	7 PVP XL	5.0%	5.0%
	8 Aerosil 200	0.2%	0.2%
	9 magnesium stearate	0.5%	0.5%

Table 3

Preparation of the "Inner" Phase

Processing Step	Machines	Process Parameter
1. dry mixing	high shear mixer Diosna P10[a]	2 min impeller: 167 U min^{-1} chopper: 3000 U min^{-1}
2. wetting and kneading	high shear mixer Diosna P10[a]	30 sec; then scaping, addition of water, kneading impeller: 167 U min^{-1} chopper: 3000 U min^{-1}
3. deagglomeration	3 mm manual screen	
4. drying	fluidized bed dryer Strea 1[b]	60°C 25–50 min as required
5. moisture content	Mettler infrared dryer LP 16[c]	10 g samples, 30 min, 105°C
6. dry sieving	classifying screening machine Frewitt MGL[d]	oszillating mode, screen: 1.25 mm mesh size; diameter of wire 0.8 mm
7. finished blend	Turbula blender T10B[e]	42 U min^{-1} in 3 l lidded drum; outer phase added via 0.8 mm manual screen, blending for 10 min.; then magnesium stearate via 0.8 mm manual screen, blending for 5 min

[a]Dierks & Söhne, D-Osnabrück.
[b]Aeromatik AG, CH-Bubendorf.
[c]Mettler Instrumente AG, CH-8606 Nänikon-Uster.
[d]Frewitt AG, CH-Fribourg.
[e]W. A. Bachofen Maschinenfabrik, CH Basel.

$$\text{friability} = \frac{\text{weight of sample - final weight}}{\text{weight of sample}} \times 100$$

The *crushing strength* of 10 tablets from each lot was determined using a Schleuniger 6 D tablet tester (Dr. Schleuniger & Co., 4501, Solothurn, Switzerland).

The *disintegration time* for 6 tablets in each case was tested in accordance with DAB 1996 using the DT 3 testing apparatus (Sotax AG, 4123 Allschwil, Switzerland).

RESULTS AND DISCUSSION

Preparation of the Granulates

The time required for kneading and drying the placebo granulates is summarized in Table 4. The paracetamol granulates required markedly less granulating fluid than did the placebo granulate. The kneading and drying times are not directly comparable.

A higher content of binder would be expected to accelerate formation of the granulate, thereby necessitating shorter kneading times, and this is precisely when happens during granulation in the high shear mixer with most of the binders tested (Table 4), the only exception being L-HPC. L-HPC presumably differs in this regard due to the high swelling capacity (10) which causes it to absorb a large amount of water, thereby delaying the wetting of the particle surfaces of other substances. In addition, the particles of binder increase in volume as swelling progresses, physically separating the particles to be bound.

The drying time in the fluid-bed dryer also depends on the amount of binder used (Figure 1). In the case of PVP, HP-M, and Lycatab DSH, the higher the binder concentration, the shorter the drying time. On the other hand, the drying time remains constant or even increases slightly when the amount of Lycatab PGS or L-HPC is increased. In both of these cases, this is also due to the large water-absorbing capacity of the binders, which precludes a rapid drying time. As a kinetic factor, drying time is nevertheless also highly dependent on particle size distribution and other particle properties (porosity, particle shape, and surface properties).

Properties of the Granulates

Particle Size Distribution

Figure 2 (below) shows the particle size distribution of the placebo granulates. The values reported for total

Table 4

Kneading and Drying Times of Granulates

Binder	Proportion of Binder	Placebo Kneading Time (s)	Placebo Drying Time (min)	Placebo Water Content (%)	Paracetamol Amount of Water (%)	Paracetamol Kneading Time (s)	Paracetamol Water Content (%)	Paracetamol Drying Time (min)
Without binder	—	240	49.0	2.5	29.5	30	0.3	32
PVP K30 PH	2%	240	37.0	2.5	26.7	30	0.5	30
	6%	90	34.5	2.5	24.4	20	0.9	30
	10%	30	24.0	3.1	11.1	210	1.6	17
Cellulose HP-M 603	2%	180	32.0	2.0	18.1	360	0.4	28
	6%	90	25.0	1.8	16.7	150	0.6	23
	10%	60	25.0	2.6	16.7	90	0.5	23
Lycatab PGS	2%	240	38.0	2.1	18.1	150	0.5	29
	6%	120	37.0	2.5	18.1	150	0.8	29
	10%	90	39.0	3.2	18.1	150	1.4	37
Lycatab DSH	2%	240	45.0	2.4	13.9	120	0.5	24
	6%	90	42.0	2.5	13.9	120	0.8	23
	10%	30	40.0	2.8	13.9	120	0.8	25
L-HPC Type: LH11	2%	170	44.0	2.1	16.7	90	0.4	27
	6%	150	40.0	2.9	16.7	90	0.7	33
	10%	180	42.0	3.2	16.7	90	0.9	33

residues are 16% (oversize particles), the median (R 50%), and the percentage of fine particles (R 84%). The values shown are the mean in each case for sieve analyses carried out in duplicate. They can be compared, in Figure 3, with the corresponding figures for sieve analysis of the paracetamol granulates.

A rise in binder concentration would lead one to expect an increase in particle size, and a large upturn

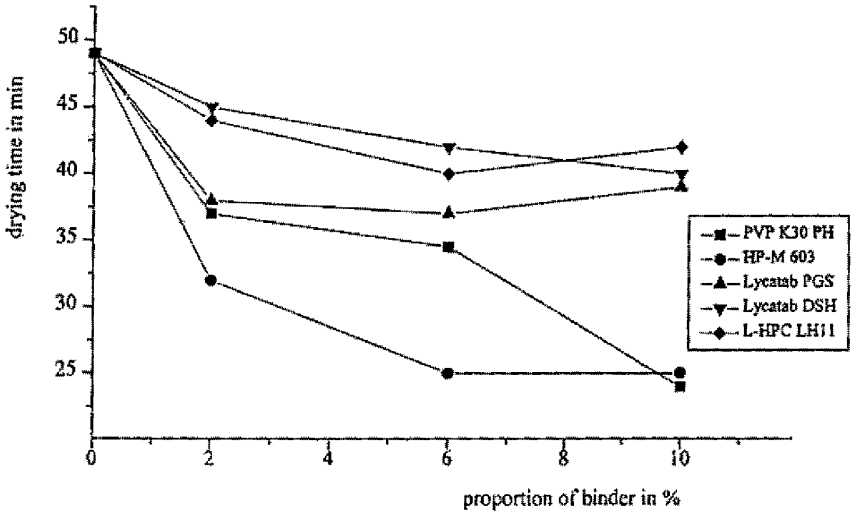

Figure 1. Drying time of placebo granulates.

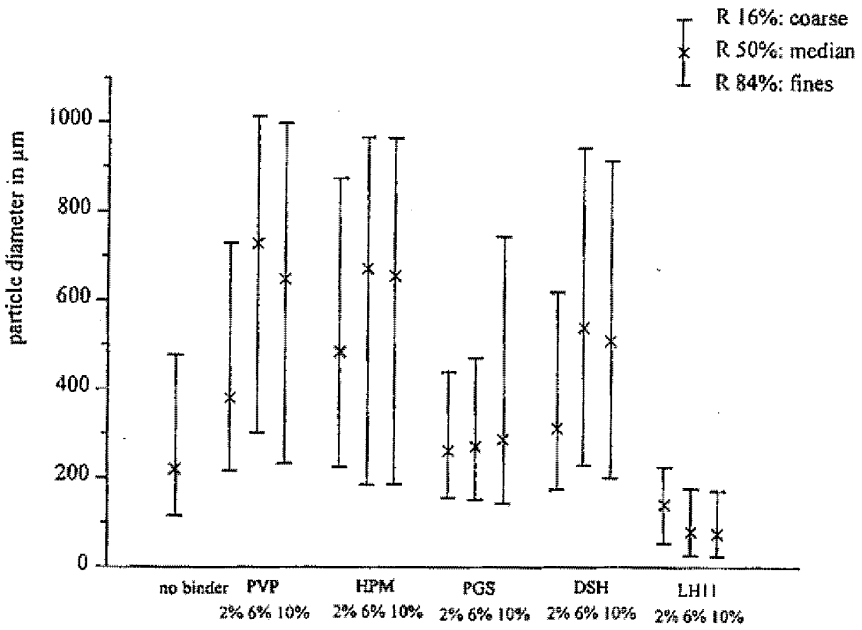

Figure 2. Particle size distributions of placebo granulates.

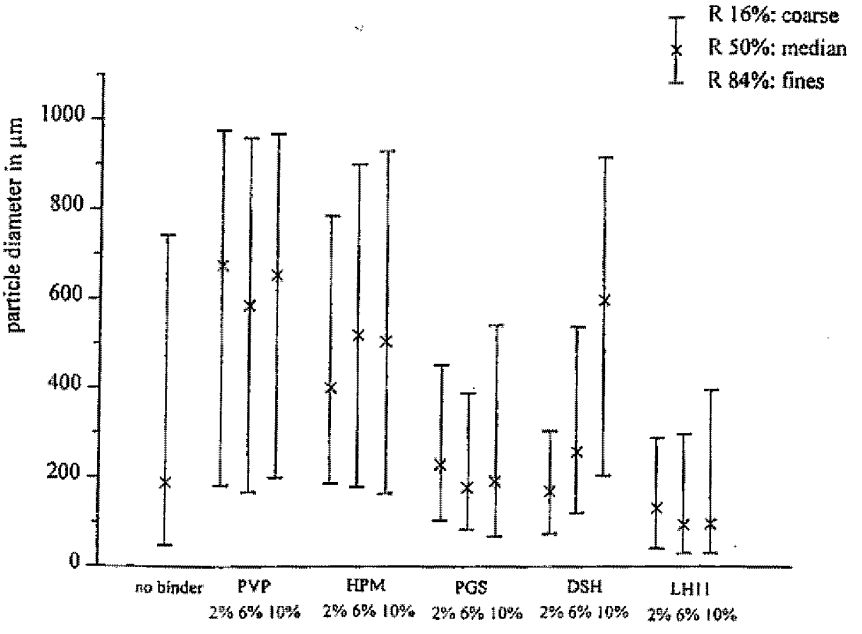

Figure 3. Particle size distributions of paracetamol granulates.

in the mean particle size (R 50%) of the placebo granulate can in fact be seen with the binders PVP K30 PH, Cellulose HP-M 603, and Lycatab DSH at concentrations of up to 6% (Figure 2). Particle size cannot be increased further when the concentration of these binders is raised (to 10%), which suggests that the binding mechanism changes above a certain critical concentration limit.

Use of L-HPC leads to a reduction in granulate particle size. This tendency continues as concentrations increase due to the small mean particle size (about 50 μm (11)) and poor binding properties of L-HPC.

The particles of paracetamol granulate are more irregular in size (Figure 3) and more oversized, but show characteristics similar to those noted for the placebo granulate.

Granule Strength

Strong granulates are advantageous for subsequent steps in the production process, such as final mixing and transport because powdery, friable granulate has a detrimental effect on flow properties and can cause demixing. For both types of granulate, and for all binder concentrations tested, the highest granule strengths were achieved using the tried and trusted binders PVP K30 PH and Cellulose HP-M 603 (Figure 4).

The binders Lycatab PGS and Lycatab DSH showed different effects in the placebo and paracetamol formulations. The granule strength of the paracetamol granulate remained constant for all 3 concentrations of Lycatab PGS but rose in the placebo granulate as concentrations of Lycatab PGS increased. However, even at a binder concentration of 10%, granule strength was lower than in granulate prepared without a binder. The maximum granule strength for paracetamol granulate is achieved with Lycatab DSH at a concentration of 10%. Granule strength is very dependent on the binder used. However, the granule strength of the placebo granulate is largely unaffected by the concentration of Lycatab DSH.

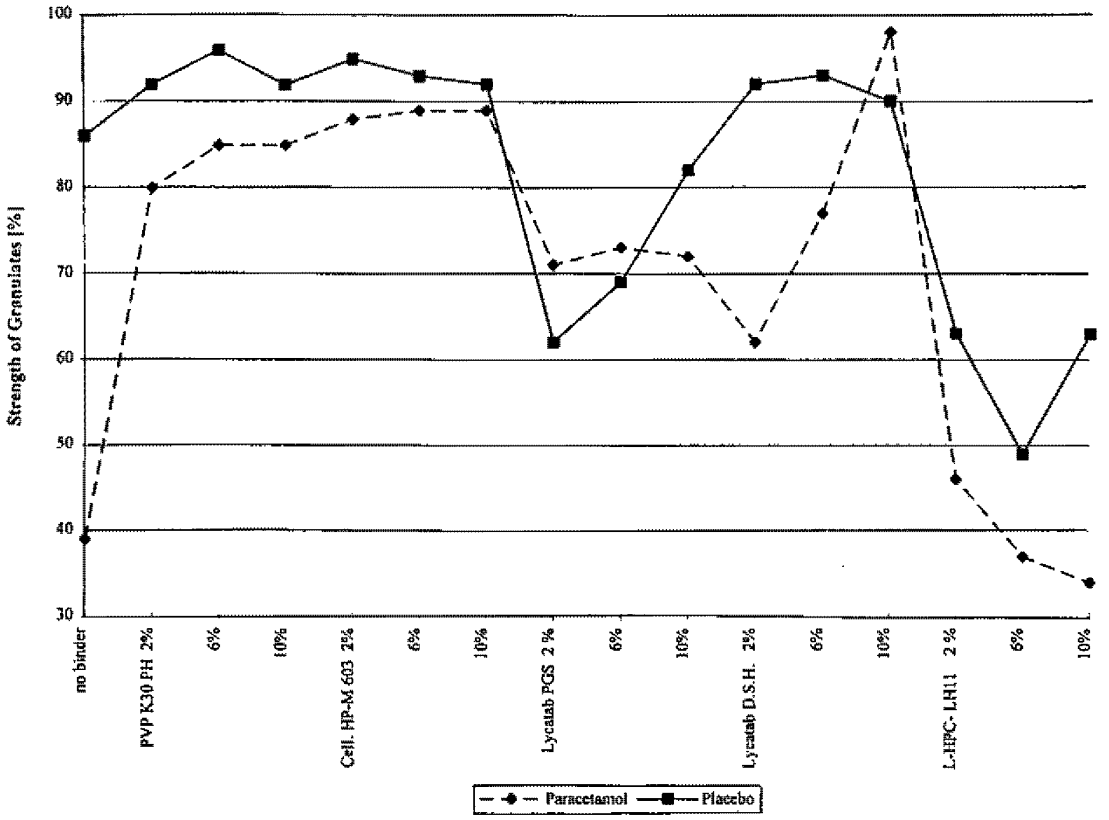

Figure 4. Strengths of placebo- and paracetamol granulates.

Granulate prepared using L-HPC shows low granule strength, in many cases even lower than that achieved when no binder is used.

Flow Properties

The flow capacity (expressed as flow angle quotients) observed in the analysis of granulate flow are shown in Figure 5. The placebo granulates proved to have very good flow characteristics with most binders. However, use of increasing concentrations of L-HPC leads to an increasing inhibition of flow, presumably due to a rise in the quantity of fine particles (Figure 2).

The relationship between flow characteristics and binder is even clearer with the paracetamol granulates. The flow characteristics of the granulate are poor without binder, but improve when even small amounts (2%) of PVP K30 PH or Cellulose HP-M 603 are added. The flow characteristics are not affected by further increases in the concentrations of these binders. Similarly good flow characteristics are achieved with Lycatab DSH at concentrations above 6%. The optimum binder concentration for Lycatab PGS is 2%, with all further additions leading to a rise in the amount of fine particles (Figure 3) and thus to reduced flow capacity. Paracetamol granulates prepared using L-HPC all flow poorly, particularly when the concentration of binder is high (compare also particle sizes in Figures 2 and 3).

Bulk and Tapped Densities

Figure 6 shows the bulk and tapped densities for the placebo granulates after 1250 taps. Figure 7 shows the corresponding results for the paracetamol granulates. Bulk and tapped densities of both sorts of granulates tend to fall as binder concentrations rise (Figures 6 and 7). This is explained by the fact that, generally speaking, larger agglomerates form. What is unusual in the

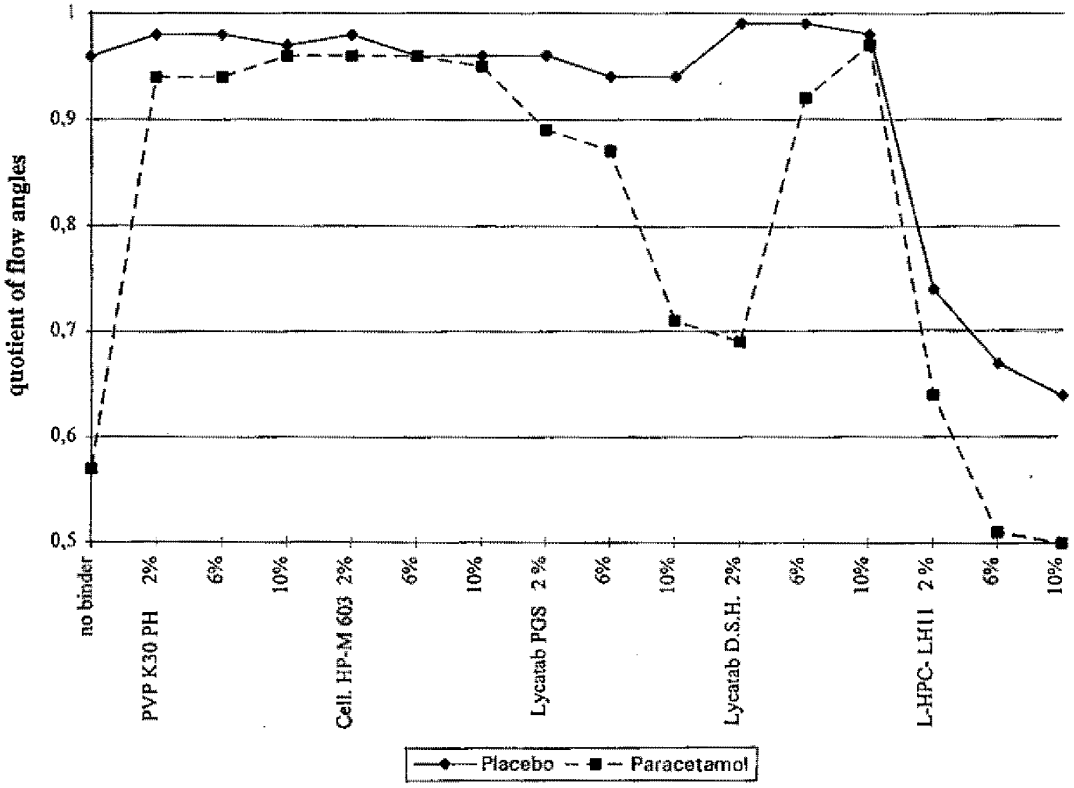

Figure 5. Flow properties of granulates (placebo and paracetamol).

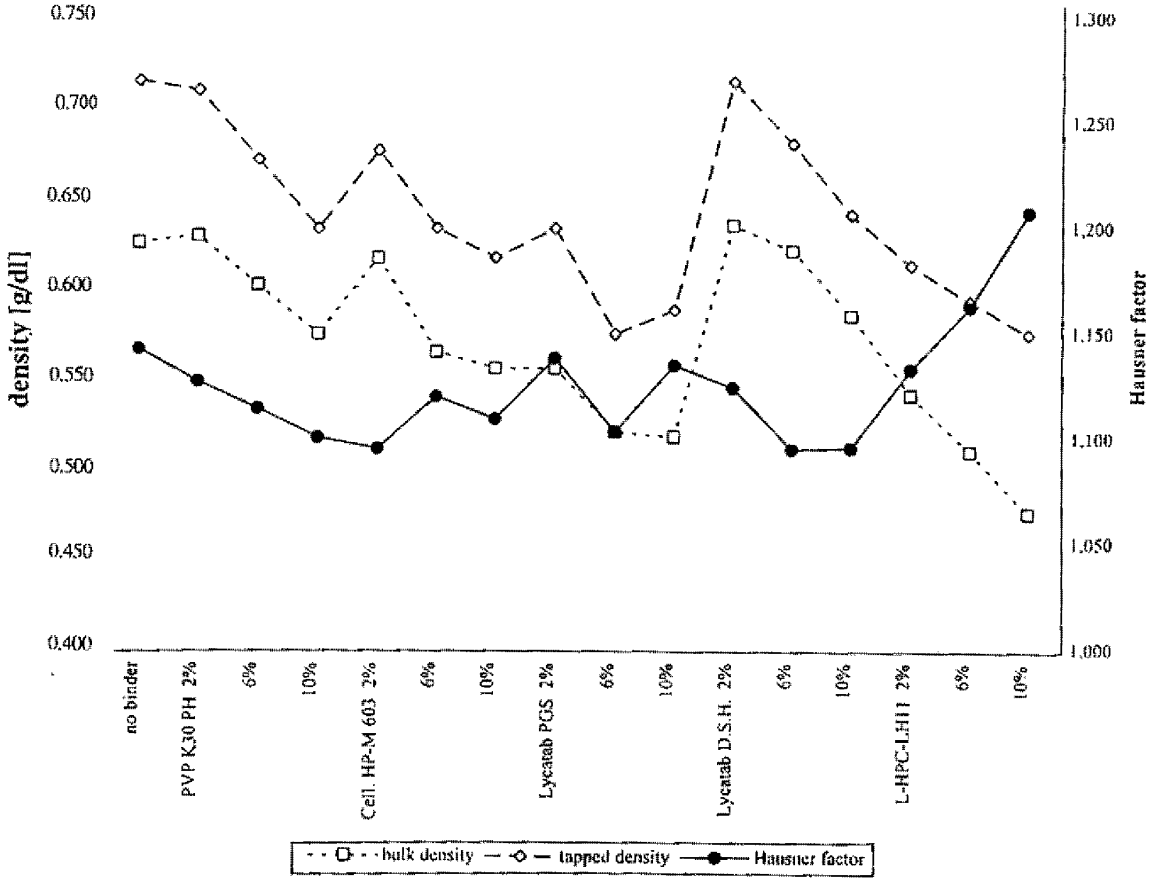

Figure 6. Bulk/tapped densities and Hausner factor of placebo granulates.

case of the L-HPC-paracetamol granulates is that all of them, despite increasing looseness as binder concentrations increase, show about the same final tapped density. This is probably related to their low granule strength (Figure 4).

The Hausner factor (the quotient of bulk density and tapped density) expresses the relative mechanical compression of the granulate (which can occur during transport or as a result of vibrations in the tablet press). It thus allows us to make inferences regarding the uniformity of particle size, shape, and crushing strength. With the help of the Hausner factor, attempts can be made at predicting both the extent of compression, and the flow problems which may occur during tabletting. With the exception of granulates containing high concentrations of L-HPC, the granulates tested had a Hausner factor lower than 1.2, and were thus within a range in which no problems were to be expected.

Tablet Properties

Crushing Strength

Figures 8 and 9 show profiles for compaction force and tablet crushing strength in relation to the binder used.

Even *placebo* granulate without binder could be processed into tablets with a good relationship between compaction force and crushing strength (Figure 8). Above a compaction force of 7.5 kN, an adequate crushing strength of 50 N is achieved for tablets with the selected diameters. The addition of binders did not necessarily lead to an increase in crushing strength. For

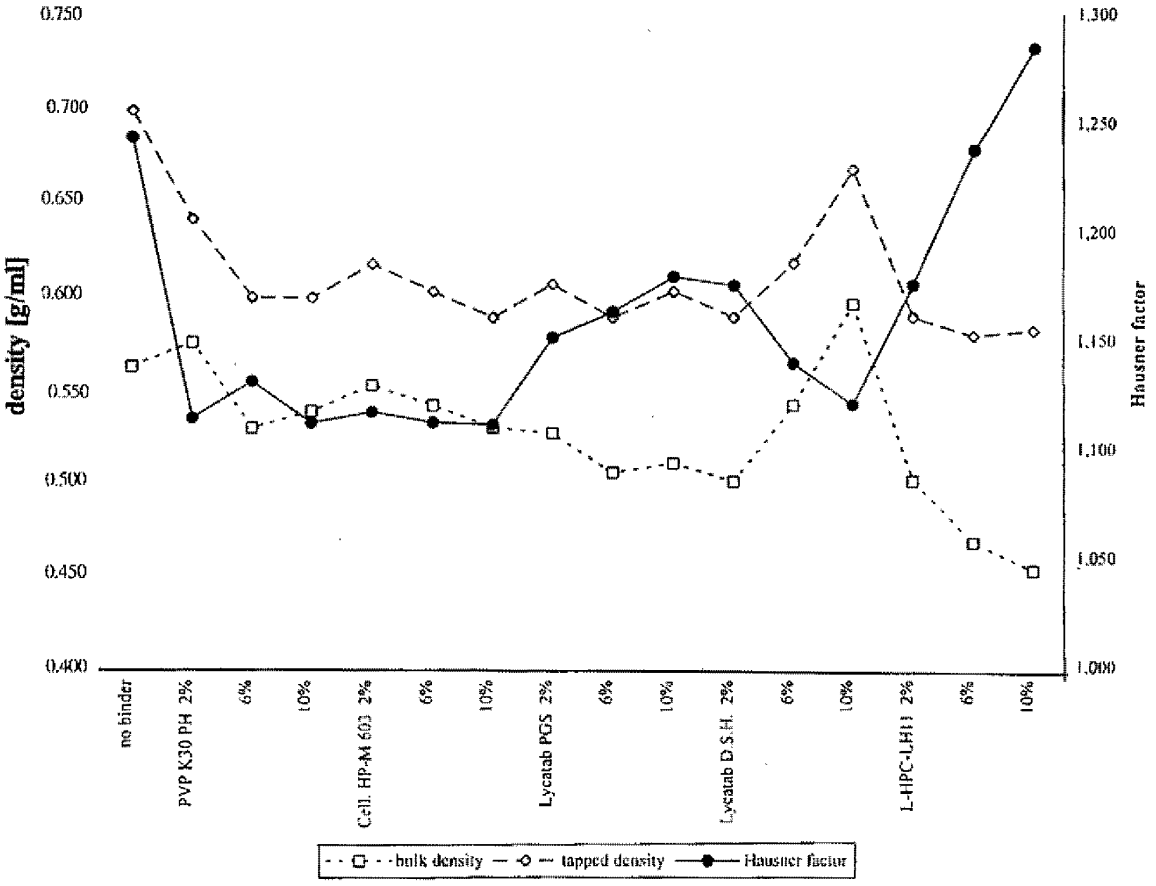

Figure 7. Bulk/tapped densities and Hausner factor of paracetamol granulates.

example, use of low concentrations of the binders PVP K30 PH, Cellulose HP-M 603, and Lycatab DSH (2% and, in the case of PVP K30 PH, 6% as well) led to a reduction in crushing strength. Use of Lycatab PGS at a concentration of 2% and Lycatab DSH at a concentration of 6% yielded crushing strength comparable to that of a granulate lacking a binder (cf. similar results in (12)). Only L-HPC at a low concentration improved crushing strength (by about 30%) as compared with the binder-free placebo formulation. PVP K30 PH does not bring about a similar rise in crushing strength until the concentration is 10%.

Cellulose HP-M 603 (6% and 10%), Lycatab DSH (10%), and Lycatab PGS (6%) can be characterised as differing very little from each other. These binders increase crushing strength by an average of 45%. The largest rise in crushing strength, approximately 75%, is achieved with a 10% concentration of the binder Lycatab PGS, which is also the concentration recommended by the manufacturer for raising crushing strength (13).

The *paracetamol tablets* without binder (Figure 9) show poor crushing strength and also are prone to capping, regardless of the compaction force applied. They are improved by the addition of binders (except for 2% L-HPC). As expected, differences relating to the type and concentration of binder are greater in this problematic formulation than in placebo. Cellulose HP-M 603 and PVP K30 PH are best here. Adequate crushing

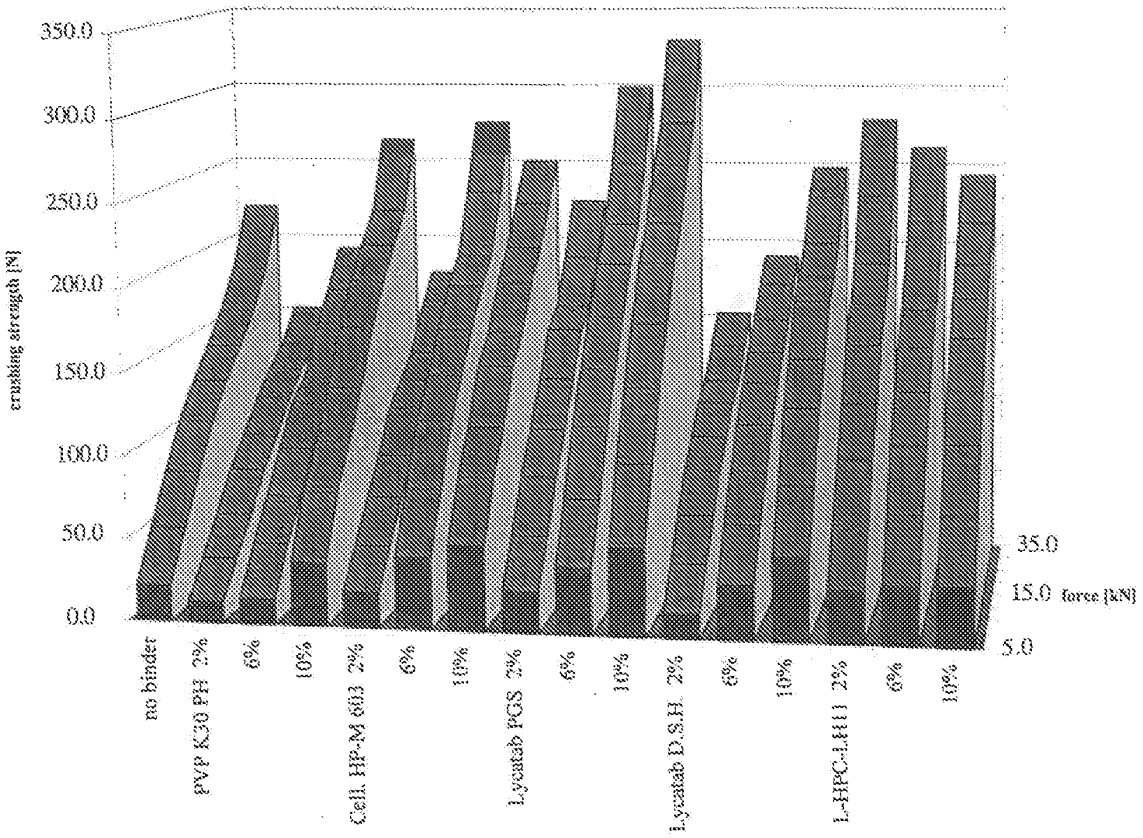

Figure 8. Compression force vs. crushing strength profile of placebo tablets.

strength is achieved with these binders even at a concentration as low as 6%, and when tablets are produced using a low compaction force.

The binders Lycatab PGS and Lycatab DSH have nearly equal binding capacity in concentrations up to 6%. At higher concentrations, Lycatab PGS shows better binding capacity. The minimum concentrations of either of these binders should not be less than 10% in the paracetamol formulation discussed here. This recommendation is based on the large amount of drug substance and poor tableting properties (capping) of the paracetamol tablets. With other model formulations based on mixtures of lactose and starch, which have fewer problematic properties, there is reason to believe that an increase in binder content above the maximum of 6% investigated here could make possible further improvement in crushing strength (14). A binder concentration of 5% has been described as adequate for tablets containing a filler of anhydrous lactose and a 10% formulation of drug substance (hydrochlorothiazide) (15).

Improvement in tablet crushing strength was comparable for L-HPC, at concentrations of 6% and 10%, Lycatab PGS (6%), and Lycatab DSH (6%).

Friability

Another important mechanical property of tablets is friability (see Figures 10 and 11). When regarding the figures, keep in mind that the scale for compaction force

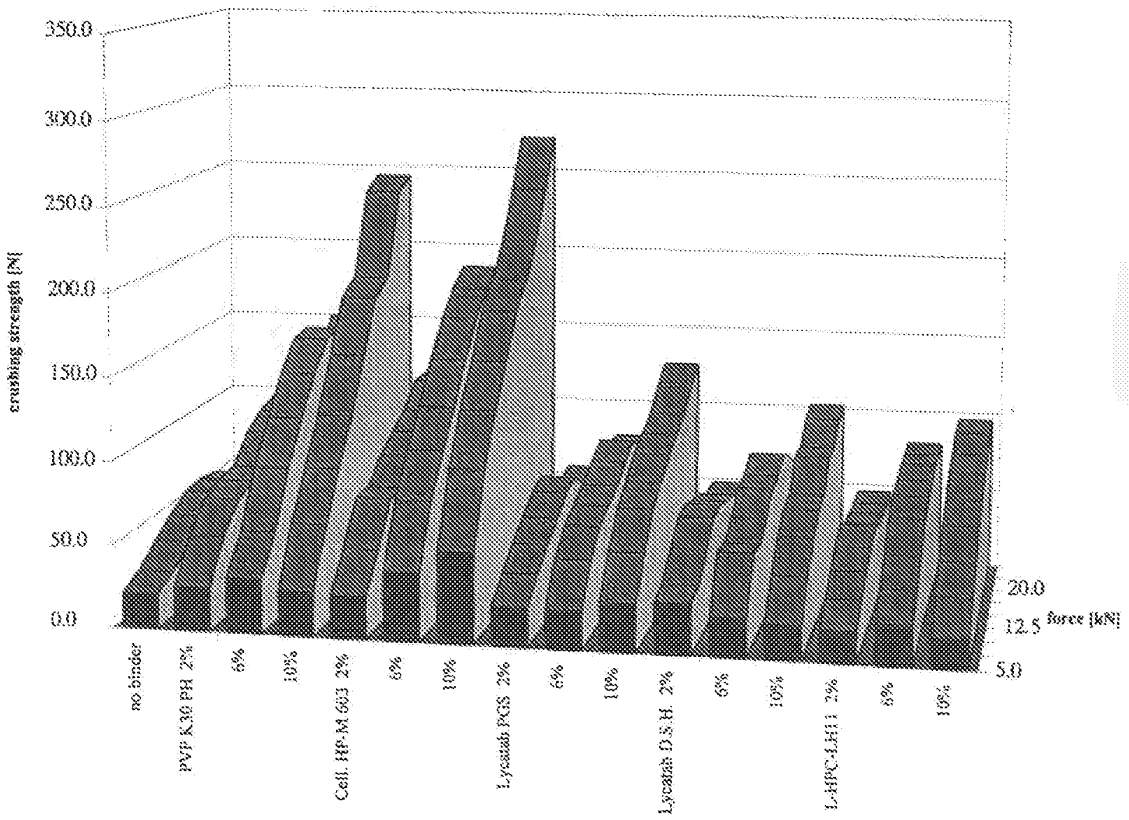

Figure 9. Compression force vs. crushing strength profile of paracetamol tablets.

begins at the rear of the graph and moves forward. To enhance the intelligibility of the chart, no bars were drawn in for friability in excess of 2% (a degree of friability which would no longer be acceptable in practice).

For all placebo formulations, friability was low when compaction force was 7.5 kN or higher, but the friability of the paracetamol tablets was often high. Sufficiently abrasion-resistant tablets (usually understood to mean tablets with a friability of no more than 1%) could only be prepared using PVP and HP-M 603.

Disintegration Times

The disintegration time of the tablets is of critical importance of their efficacy. Although an effective "disintegrant" is added to the outer phase before tableting, there are considerable differences in disintegration times. Figure 12 compares the disintegration times of placebo tablets produced under different compaction forces, while Figure 13 provides similar information on paracetamol tablets. It can be seen that it is in fact the tried and trusted binders (PVP and HP-M 603) which delay disintegration. Lycatab DSH has the same effect.

Binder Effectiveness

Binder effectiveness refers to the degree to which the lowest possible concentration of a binder can contribute to the optimization of *all* granulate and tablet properties. For granulates, these properties include in particular flow characteristics, crushing strength, and mean particle size. The tablet property most strongly affected is crushing strength.

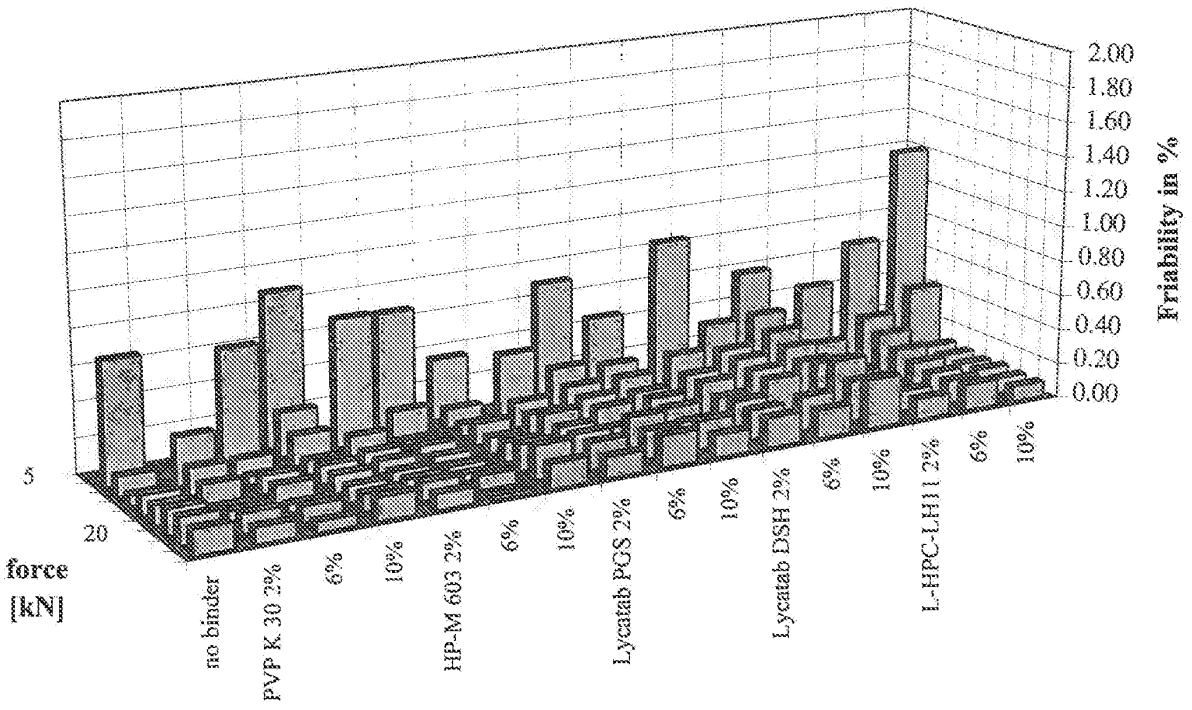

Figure 10. Friability of placebo tablets.

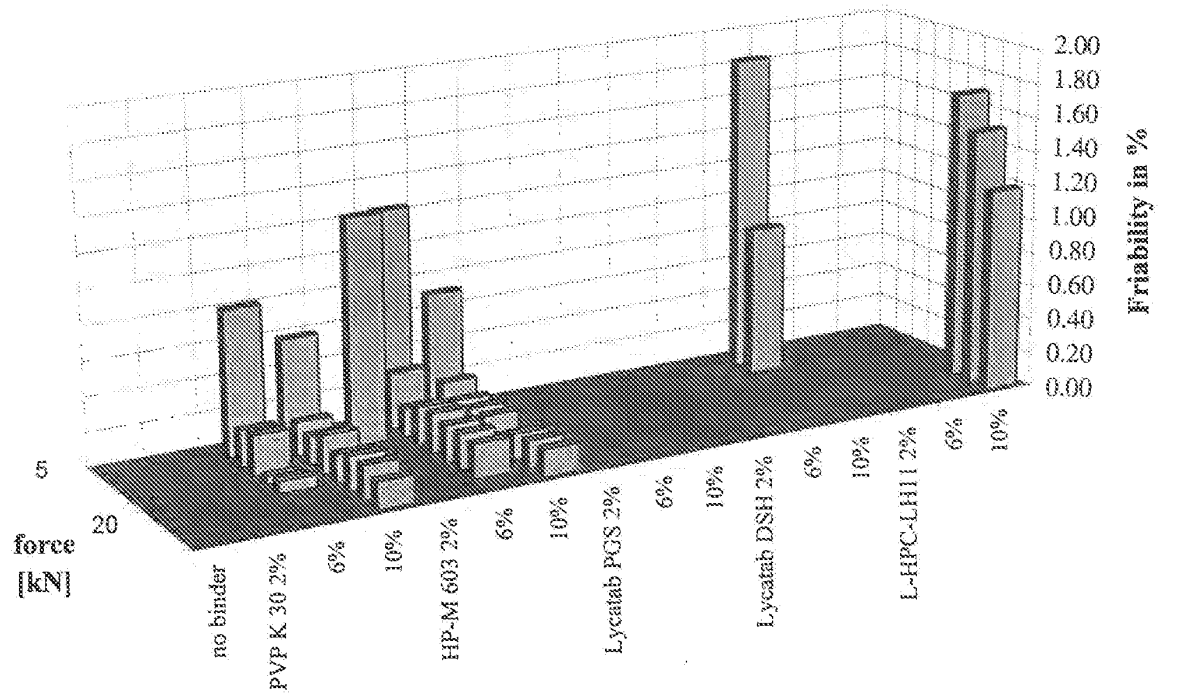

Figure 11. Friability of paracetamol tablets.

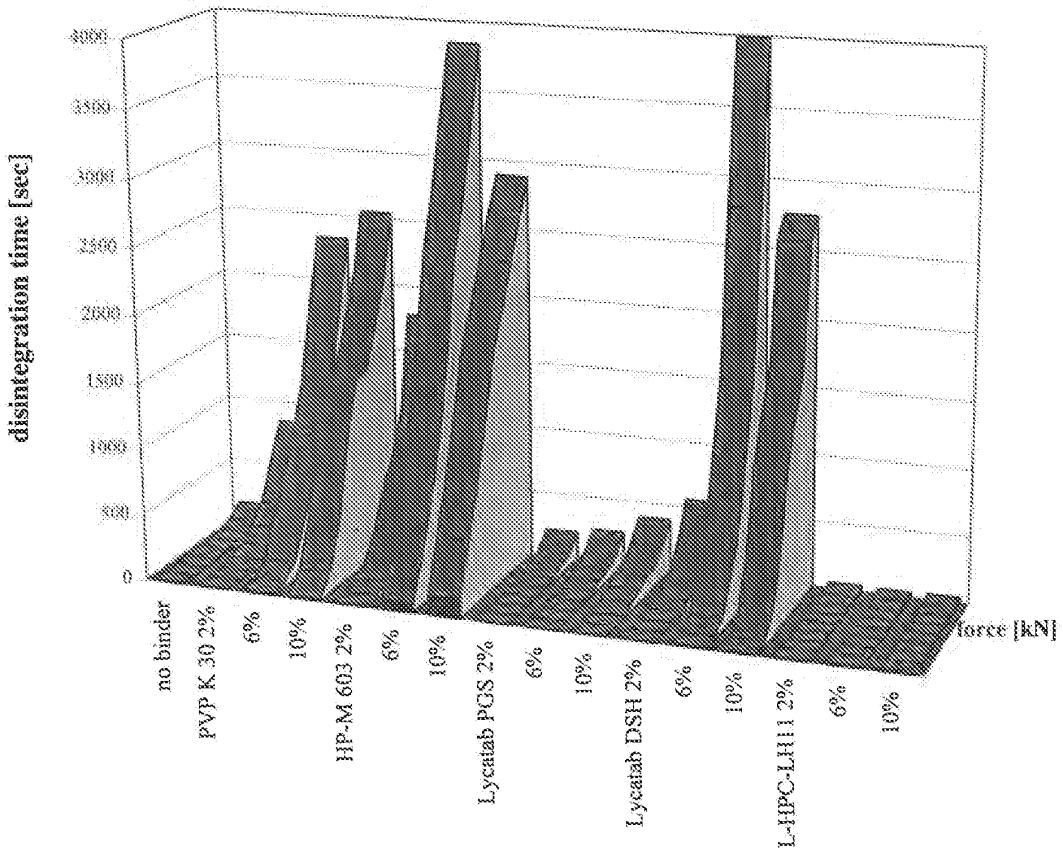

Figure 12. Disintegration time of placebo tablets.

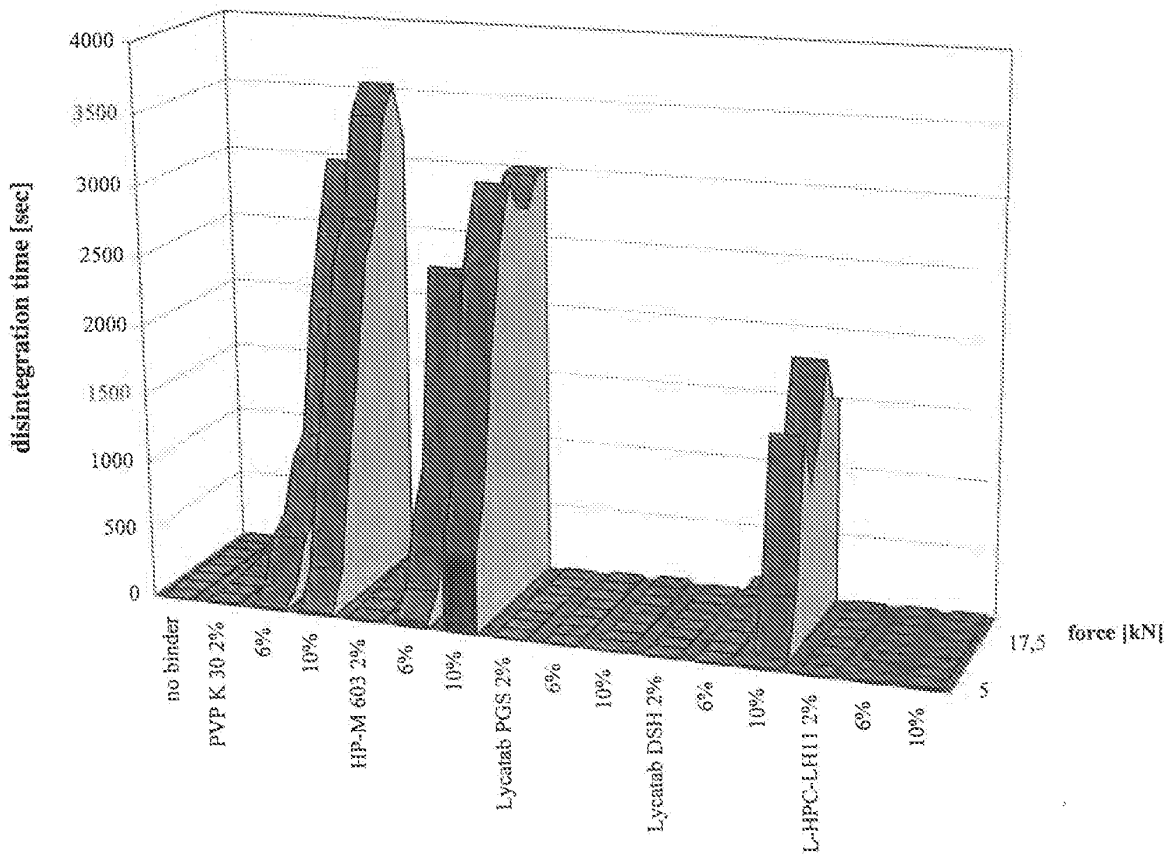

Figure 13. Disintegration time of paracetamol tablets.

Table 5

Effect of Binder on Some Properties of Granulates and Tablets: Binder Effectiveness

Binder	Proportion of Binder	Particle Size (R 50%)	Flow-ability	Granulate Strength	Tablet Crushing Strength
PVP K30 PH	2%	166%	33%	56%	18%
	6%	221%	33%	65%	65%
	10%	221%	35%	62%	121%
Cellulose HP-M 603	2%	117%	35%	68%	33%
	6%	191%	34%	68%	120%
	10%	183%	33%	68%	163%
Lycatab PGS	2%	20%	28%	27%	11%
	6%	9%	25%	34%	46%
	10%	16%	11%	40%	83%
Lycatab DSH	2%	16%	12%	33%	-6%
	6%	90%	32%	53%	26%
	10%	174%	36%	78%	54%
L-HPC Typ: LH11	2%	-34%	-5%	-4%	11%
	6%	-57%	-20%	-24%	35%
	10%	-58%	-23%	-20%	37%

The present assessment has been restricted to these features in order to allow conclusions about binder effectiveness in different formulations to be drawn more easily.

For the graphs, the results obtained with binder-free placebo and drug preparations were taken as reference values and set at zero. The percentage deviations of the properties of the other granulates and tablets were always calculated in relation to these reference values. The arithmetic mean of the values obtained was then calculated for both the placebo and paracetamol granulates (Table 5) and plotted (Figure 14).

PVP K30 PH and Cellulose HP-M 603 show the greatest binder effectiveness. A 10% concentration of Lycatab DSH can be used as an alternative.

The main effect of Lycatab PGS is the improvement of tablet crushing strength. Although L-HPC worsens granulate properties, it nevertheless improves tablet crushing strength to some extent.

CONCLUSIONS

Use of the standard binders PVP and Cellulose HP-M 603 makes possible the manufacture of tablets with the best mechanical properties but the worst disintegration times. Hydroxypropylmethylcellulose in particular is used in granulate formulations to achieve delayed release (16). Lycatab PGS has fewer soluble components than other pre-gelatinized maize starches currently on the market (17) and is therefore expected to have a relatively good disintegrating effect (18). This has been confirmed in the present study.

Lycatab DSH is spray-dried maltodextrin and dissolves completely in water. According to the manufacturer, it is not supposed to interfere with disintegration and dissolution at recommended concentrations of 2-10%, and it is supposed to promote good flow in granulates and hardness in tablets. This claim was not necessarily confirmed, particularly because the disintegration time of the placebo tablets was markedly increased. And the advantage of a lactose-starch formulation over PVP in improving the relationship between crushing strength and disintegration, noted by Delacourte et al. (19), could not be verified here over the entire range of binder concentration and compaction force, either for placebo or for paracetamol. At a 10% concentration, however, Lycatab DSH can be substituted for PVP or HP-M 603.

When L-HPC is used as a dry binder, its small particle size makes it particularly suitable for the manufacture of hard tablets. Thanks to its high swelling capacity (greater that of PVP XL, which is used as a

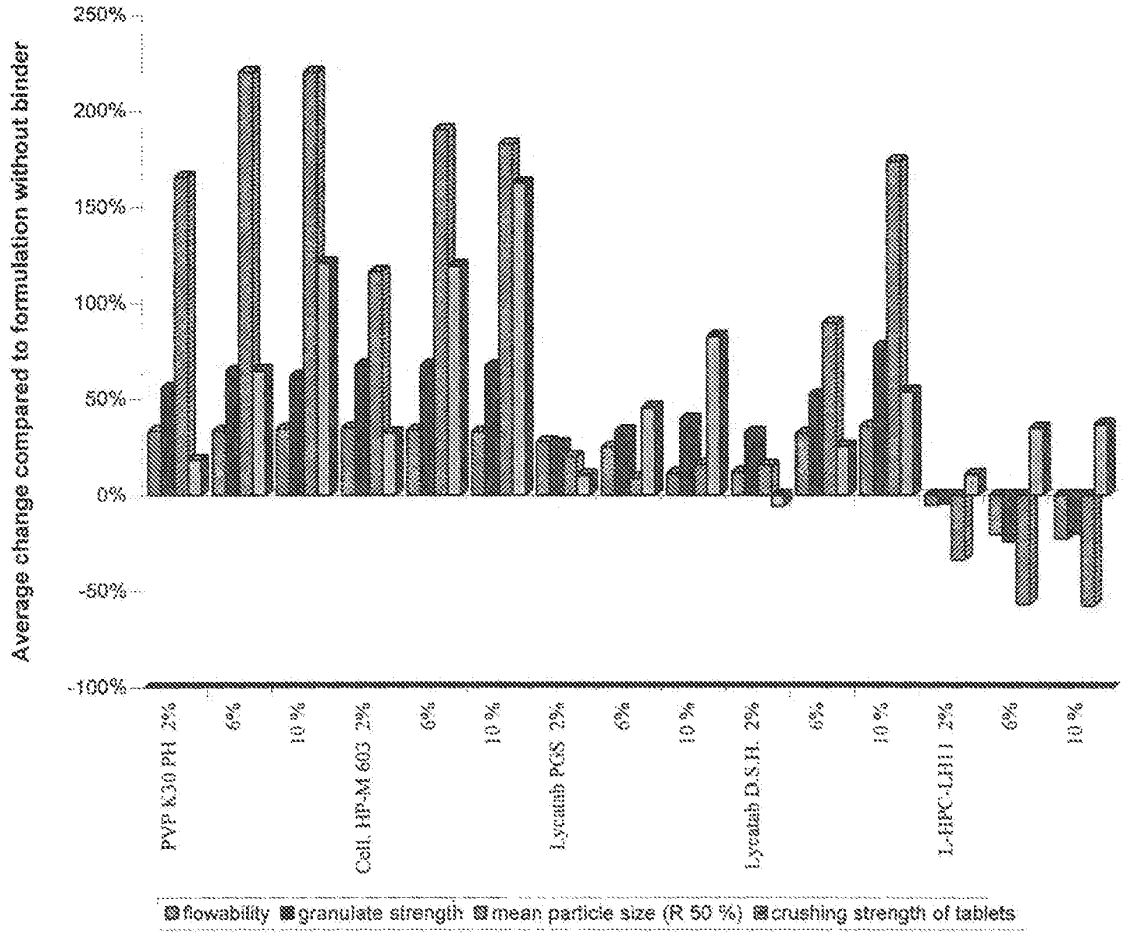

Figure 14. Binder efficiency.

disintegrant (20)), it reduces the disintegration time of tablets even after wet granulation. However, it shows little binding efficacy in granulates.

ACKNOWLEDGMENTS

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20. Brochure from ShinEtsu, Low-Substituted Hydroxypropyl Cellulose, p. 7, Fig. 3 and Fig. 4.

PATENT
Attorney Docket No. 05273.0147-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
	)
Kazuyuki FUJIHARA	) Group Art Unit: 1627
	)
Application No.: 11/919,678	) Examiner: Sarah Pihonak
	)
Filed: October 31, 2007	)
	) Confirmation No.: 6965
For: PHARMACEUTICAL COMPOSITION	)
	) **VIA EFS-WEB**

Commissioner for Patents
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Alexandria, VA 22313-1450

Commissioner:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(b)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicant brings to the attention of the Examiner the listed documents on the attached IDS Form ("Form"). This Information Disclosure Statement is being filed before the mailing date of a first Office Action after the filing of a Request for Continued Examination in the above-referenced application.

Copies of the listed non-patent literature documents are attached.

Applicant respectfully requests that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached Form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed

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Applicant further reserves the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 17, 2014

By: Charles E Van Horn

Charles E. Van Horn
Reg. No. 40,266
(202) 408-4000

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	11/919,678
				Filing Date	October 31, 2007
				First Named Inventor	Kazuyuki FUJIHARA
				Art Unit	1627
				Examiner Name	Sarah PIHONAK
Sheet	1	of	1	Attorney Docket Number	05273.0147-00000

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		Request for Invalidation from invalidity proceedings in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), August 5, 2012.	Yes
		Bi Dianzhou, Pharmaceutics, Edition 4, Beijing: People's Medical Publishing House, February 2003.	Yes
		"Application and Effect of Pregelatinized Starch in Tablets," Chinese Pharmaceutical Information, Vol.16, Issue 7, 2000, published in 2000	Yes
		"Use of Pregelatinized Starch in Tablet Manufacturing," Chinese Pharmaceutical Journal, Vol. 29, Issue 4, April 1994, published in April 1994.	Yes
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		"*In Vitro* Dissolution and Bioavailability of Acyclovir Capsules Formulated with Pregelatinized Starch," Chinese Journal of Pharmaceuticals, 1998, 29(5), published on May 20, 1998.	Yes
		Dissolution of Drug Solid Preparation, "Factors Influencing Dissolution Rates," Wu Guangchen, Yue Zhiwei, People's Medical Publishing House, published in October 1994.	Yes
		Reply Brief from invalidity proceedings in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), October 25, 2012.	Yes
		Examination Decision on the Request for Invalidation in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), April 26, 2013.	Yes

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First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	22852
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PATENT
Attorney Docket No. 05273.0147-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Kazuyuki FUJIHARA	)	Group Art Unit: 1627
	)	
Application No.: 11/919,678	)	Examiner: Sarah Pihonak
	)	
Filed: October 31, 2007	)	
	)	Confirmation No.: 6965
For: PHARMACEUTICAL COMPOSITION	)	
	)	**VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

THIRD SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. § 1.114

Further to the December 6, 2013, Supplemental Amendment, and January 17, 2014, Second Supplemental Amendment filed in this application, Applicant submits this Third Supplemental Amendment under 37 C.F.R. § 1.114.

Please amend this application as follows:

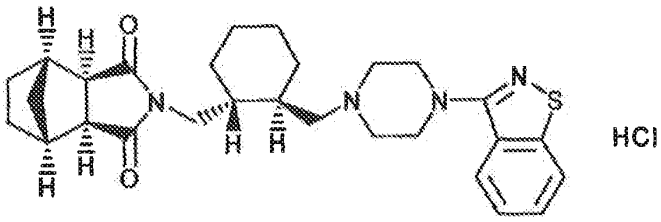
Amendments to the Claims being at page 2 of this paper.

Remarks/Arguments follow the amendment section.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder; wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt), and the pregelatinized starch is incorporated in an amount of ~~10~~ 20 to 50% (wt/wt) based on the weight of the preparation.

2. (Canceled).

3. (Canceled).

4. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose.

5-8. (Canceled).

9. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation.

10-11. (Canceled).

12. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 10 to 160 mg.

13. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 120 mg.

14. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 40 to 120 mg.

15. (Canceled).

16. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose and a content of lurasidone in the preparation is 25 to 40% (wt/wt).

17-19. (Canceled).

20. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation and a content of lurasidone per tablet is 40 to 120 mg.

21. (Previously Presented) The oral preparation of claim 1 wherein a pregelatinizing ratio of the pregelatinized starch is 50 to 95%.

22. (Previously presented) The oral preparation of claim 1 wherein a 50% by volume particle size of lurasidone is 0.1 to 8 μm.

23. (Previously Presented) The oral preparation of claim 1 wherein the pregelatinized starch contains water soluble matter of 30% or less.

24. (Canceled).

25. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble excipient is mannitol or lactose, the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation, and a content of lurasidone per tablet is 20 to 120 mg.

26. (Previously Presented) The oral preparation of claim 9 wherein the water-soluble excipient is mannitol or lactose.

27. (Canceled).

28. (Previously Presented) The oral preparation of claim 1 wherein the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose.

29. (Previously Presented) The oral preparation of claim 1 wherein a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

30. (Previously Presented) The oral preparation of claim 1, further comprising a disintegrant wherein a content of the disintegrant per tablet is 0.5 to 5% (wt/wt).

31. (Currently Amended) The oral preparation of claim 1, further comprising a disintegrant wherein

a content of the disintegrant per tablet is 0.5 to 5% (wt/wt);

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation;

a content of lurasidone per tablet is 40 to 120 mg;

a pregelatinizing ratio of the pregelatinized starch is 50 to 95%;

50% by volume particle size of lurasidone is 0.1 to 8 μm;

the pregelatinized starch contains water soluble matter of 30% or less;

the water-soluble excipient is mannitol or lactose~~, and a content of the water-soluble excipient per tablet is 30 to 80% (wt/wt)~~;

the water-soluble polymer binder is hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone or hydroxypropylcellulose; and

a content of the water-soluble polymer binder per tablet is 0.5 to 10% (wt/wt).

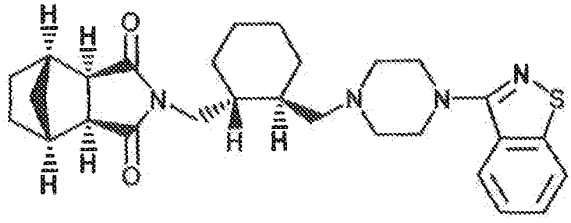
32. (Previously Presented) The oral preparation of claim 1 wherein a content of lurasidone per tablet is 20 to 160 mg.

33. (Canceled).

34. (Previously Presented) The oral preparation of claim 1, wherein a similarity factor f2 of each preparation is in the range of 50≤f2≤100 when a content of lurasidone per tablet changes over a range of 20 to 120 mg.

35-36. (Canceled).

37. (Currently Amended) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



(1),

a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, wherein the oral preparation contains 20 to 45% (wt/wt) of lurasidone, the oral preparation contains 20 mg to 120 mg of lurasidone, the pregelatinized starch is incorporated in an amount of ~~10~~ 20 to 50% (wt/wt) based on the weight of the oral

preparation, and the oral preparation exhibits an equivalent dissolution profile across the range of lurasidone per oral preparation.

38. (Previously Presented) The oral preparation of claim 1, wherein the water-soluble excipient is one or more selected from the group of mannitol, lactose, saccharose, sorbitol, D-sorbitol, erythritol and xylitol.

39. (Previously Presented) The oral preparation of claim 30, wherein the disintegrant is one or more selected from the group of com starch, crystalline cellulose, low substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethyl starch sodium and crospovidone.

40. (Previously Presented) The oral preparation of claim 1, further comprising a lubricant, wherein a content of the lubricant per tablet is 1.0% (wt/wt) to 1.43% (wt/wt).

41. (Previously Presented) The oral preparation of claim 40, wherein the lubricant is selected from the group of magnesium stearate, talc, polyethylene glycol, silica and hydrogenated vegetable oil.

42. (Previously Presented) The oral preparation of claim 1, wherein the oral preparation is a tablet.

43. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1′R,2′S,3′R,4′S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone), a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt),

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation,

the water-soluble excipient is mannitol or lactose, and

the water-soluble polymer binder is one or more agents selected from the group of hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and polyvinyl alcohol.

44. (Previously Presented) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone), a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder, and further comprises a disintegrant and a lubricant, wherein a content of lurasidone in the preparation is 20 to 45% (wt/wt),

the pregelatinized starch is incorporated in an amount of 20 to 30% (wt/wt) based on the weight of the preparation,

the water-soluble excipient is mannitol,

the water-soluble polymer binder is hydroxypropylmethylcellulose, and

the oral preparation is a tablet.

45. (Canceled).

REMARKS

I. Status of Claims

Following entry of the Amendment, claims 1, 4, 9, 12-14, 16, 20-23, 25, 26, 28-32, 34, and 37-44 (4 independent claims and 27 total claims) will be pending. The Examiner telephoned Applicant's representative on January 22, 2014, proposing that Applicant change the lower limit of the pregelatinized starch in claims 1 and 37 from 10% (wt/wt) to 20% (wt/wt), delete the recitation regarding the amount of water-soluble excipient from claim 31, and cancel claims 27 and 45 in order to place the above-identified application in condition for allowance. To comply with the Examiner's proposals and solely for the purpose of placing this application in condition for allowance, claims 1, 31, and 37 are amended, and claims 27 and 45 are canceled herein. Applicant is not disclaiming any subject matter by the amendments provided herein, and reserves the right to file a continuation application with claims that include the canceled subject matter.

The specification, *e.g.*, ¶¶[0022], [0023] of U.S. Patent Application Publication No. 2009/0143404 A1 ("the '404 publication"), which is the publication of the present application, provides written description support for the amended claims. Accordingly, no new matter is added by the amendments provided herein. Entry of the amendments is respectfully requested.

II. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

If there is any fee due in connection with the filing of this Supplemental Amendment, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 24, 2014

By: Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266
(202) 408-4000

Electronic Acknowledgement Receipt

EFS ID:	18022499
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	Pharmaceutical composition
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	22852
Filer:	Charles E. Van Horn/Charlene Woods
Filer Authorized By:	Charles E. Van Horn
Attorney Docket Number:	05273.0147-00000
Receipt Date:	24-JAN-2014
Filing Date:	31-OCT-2007
Time Stamp:	17:39:21
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Third_Supplemental_Amendment.pdf	359999 d0fada65a1e152cc2f89c343a9277aeb7590aedb	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	7
	Applicant Arguments/Remarks Made in an Amendment	8	9
Warnings:			
Information:			
	Total Files Size (in bytes):	359999	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

22852 7590 02/03/2014

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER
PIHONAK, SARAH

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 02/03/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	05273.0147-00000	6965

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	05/05/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22852 7590 02/03/2014

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	05273.0147-00000	6965

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	05/05/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-254020

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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22852 7590 02/03/2014

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 02/03/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 276 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 276 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	11/919,678	FUJIHARA, KAZUYUKI	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *SARAH PIHONAK*. (3)_____.

(2) *JENNIFER GUPTA*. (4)_____.

Date of Interview: *27 January 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,4,9,12-14,16,20-23,25,26,28-32,34 and 37-44*.

Identification of prior art discussed: *Fujihara et. al. & Salpekar et. al.*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

A proposed examiner's amendment was discussed. Applicants submitted supplemental claim amendments on 1/24/14. Claims 1, 4, 9, 12-14, 16, 20-23, 25-26, 28-32, 34, and 37-44 as amended on 1/24/14, are allowed.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/SARAH PIHONAK/ Examiner, Art Unit 1627	

Notice of Allowability	Application No. 11/919,678	Applicant(s) FUJIHARA, KAZUYUKI	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *1/24/2014*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,4,9,12-14,16,20-23,25-26,28-32,34,37-44*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☒ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *1/27/2014* .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARAH PIHONAK/
Examiner, Art Unit 1627

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

This application, filed 10/31/2007, is a national stage entry of PCT/JP2006/310571, filed on 5/26/2006.

Request for Continued Examination

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/11/2013 has been entered.

Response to Remarks

3. Claims 1, 4, 9, 12-14, 16, 20-23, 25-26, 28-32, 34, and 37-44 are currently pending as of the supplemental reply and amendments filed on 1/24/2014.

A track one request has been granted for this application.

Claims 1-4, 9, 11-14, 16, 19-34, and 37 were previously rejected under 35 USC 103(a) as being unpatentable over Fujihara et. al., EP 1327440, in view of Salpekar et. al., USP 4,600,579. The Applicants have traversed this rejection and have argued that neither Fujihara nor Salpekar teach or suggest the claimed oral preparation, as Fujihara teaches that tablets comprising 16.3% or more of lurasidone have inferior dissolution profiles in comparison to tablets having lesser amounts of lurasidone. The Applicants have submitted that Fujihara does not teach the lurasidone tablets as comprising pregelatinized starch, and that the dissolution profiles presented in Fujihara show that a lurasidone tablet comprising 29.0% of lurasidone had a percent dissolution of only 84% at 30 minutes, while tablets having less than 16.3% of lurasidone had over 90% dissolution after 30 minutes. The Applicants have argued that a skilled person would not have incorporated lurasidone in a tablet preparation at an amount of 20-45% from the teachings of Fujihara, based upon the poorer dissolution profiles of tablets comprising more than 16.3% lurasidone. The Applicants have submitted that Salpekar does not provide any data showing that adding pregelatinized starch shortens dissolution time, and in fact Salpekar shows that by increasing pregelatinized starch in a tablet formulation, such as that shown in Ex. 1 of Salpekar (18.0% PGS), the disintegration time is prolonged (18 minutes) in comparison to the disintegration time for tablet formulation comprising 8.85% PGS (6 minutes). The Applicants have additionally argued that Salpekar teaches a tablet composition which comprises water soluble acetaminophen, while the instantly claimed preparation comprises water insoluble lurasidone. It has been maintained by the Applicants that a person of ordinary skill in the

art would not have looked to using PGS with a water insoluble ingredient such as lurasidone based upon the teachings of Salpekar. The Applicants have argued that the instantly claimed oral preparation has unexpected properties over the prior art, and have provided comparison data for the 30-minute dissolution values for the instantly claimed oral preparation which comprises pregelatinized starch and lurasidone and the oral preparation taught by Fujihara which comprises the same amount of lurasidone and the disintegrant croscarmellose sodium but without pregelatinized starch. The Applicants have argued that the 30-minute dissolution value of 86% for the instantly claimed preparation is significantly better than the preparation taught by Fujihara, which has a 30-minute dissolution value of 70%.

The examiner has fully considered Applicants' arguments and the supplemental claim amendments, and they are found persuasive. The rejection of claims 1-4, 9, 11-14, 16, 19-34, and 37 were previously rejected under 35 USC 103(a) as being unpatentable over Fujihara et. al., in view of Salpekar et. al., is withdrawn.

Claims 1-4, 9, 11-14, 16, 19-34, and 37 were previously rejected for obviousness type double patenting over claim 1-7 of co-pending appl. 12/997779. The claims in the co-pending application have been amended to recite specific active ingredients in the formulation which excludes lurasidone. The rejection for provisional obviousness type double patenting over the claims of 12/997779 is withdrawn in consideration of the amendments to the claims of the co-pending application.

4. Claims 1, 4, 9, 12-14, 16, 20-23, 25-26, 28-32, 34, and 37-44 are free of the prior art. A statement of reasons for allowance is disclosed below.

Reasons for Allowance

5. The following is an examiner's statement of reasons for allowance: there is no prior art which teaches or suggests the instantly claimed oral preparation which comprises from 20-45% (wt/wt) lurasidone; and from 20-50% (wt/wt) pregelatinized starch. The closest prior art is Fujihara et. al., EP 1327440; and Salpekar et. al., USP 4,600,579 (both of previous record). Fujihara et. al. teaches a tablet composition which comprises lurasidone; water soluble excipients such as mannitol or lactose; and corn starch as a disintegrant. However, Fujihara et. al. does not teach pregelatinized starch. Salpekar teaches an oral acetaminophen composition which comprises partially gelatinized starch in an amount from 5 or less to 15 or more parts per 100 parts of the composition. Salpekar does not teach the composition as comprising lurasidone. Salpekar shows comparison data for a tablet which comprises acetaminophen and about 18.0% partially gelatinized starch, having a disintegration time of 18 minutes, to a tablet which comprises acetaminophen and 8.85% partially gelatinized starch that exhibits a disintegration time of about 6 minutes. The Applicants have shown in the specification that a composition comprising 80 mg. lurasidone without pregelatinized starch as prepared according to Fujihara et. al. showed reduced percent dissolution over a period of 45 minutes in comparison to 2-40 mg. lurasidone tablets not containing pregelatinized starch, and have submitted that doubling the content of lurasidone in a tablet without pregelatinized starch results in a poorer dissolution profile (see paragraph

[0089] and Fig. 2). The Applicants have also shown that tablets comprising lurasidone (80 mg.) and pregelatinized starch in an amount of 25% wt/wt have nearly the same dissolution profile as tablets comprising lesser amounts of lurasidone (40 and 20 mg.) and 25% wt/wt pregelatinized starch (see paragraphs [0031-0035], and Fig. 3); therefore, doubling the amount of lurasidone in a tablet (from 40 mg. to 80 mg.) did not decrease the percent dissolution. The claimed oral preparation is therefore novel and non-obvious over the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 1/17/2014 was filed after the mailing date of the final office action on 12/11/2012. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Conclusion

7. Claims 1, 4, 9, 12-14, 16, 20-23, 25-26, 28-32, 34, and 37-44 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARAH PIHONAK/
Examiner, Art Unit 1627

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	11/919,678	FUJIHARA, KAZUYUKI	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

All participants (applicant, applicant's representative, PTO personnel):

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☐ Attachment

/SARAH PIHONAK/ Examiner, Art Unit 1627	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	**Art Unit**
	SARAH PIHONAK	1627

CPC		
Symbol	**Type**	**Version**
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CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**
/				
/				

/S.P./ Examiner.Art Unit 1627 (Assistant Examiner)	01/28/2014 (Date)	**Total Claims Allowed:** 27
/SARAH PIHONAK/ Examiner.Art Unit 1627 (Primary Examiner)	01/28/2014 (Date)	O.G. Print Claim(s): 1 O.G. Print Figure: None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	**Art Unit**
	SARAH PIHONAK	1627

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
514	254.02

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
544	368				

INTERNATIONAL CLASSIFICATION											
CLAIMED					**NON-CLAIMED**						
A	6	1	K	31 / 497 (2006.01.01)							
C	0	7	D	413 / 00 (2006.01.01)							
C	0	7	D	417 / 00 (2006.01.01)							
C	0	7	D	419 / 00 (2006.01.01)							

/S.P./ Examiner.Art Unit 1627 (Assistant Examiner)	01/28/2014 (Date)	**Total Claims Allowed:** 27	
/SARAH PIHONAK/ Examiner.Art Unit 1627 (Primary Examiner)	01/28/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	**Art Unit**
	SARAH PIHONAK	1627

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1		17		33										
	2		18	19	34										
	3		19		35										
2	4	8	20		36										
	5	9	21	20	37										
	6	10	22	21	38										
	7	11	23	22	39										
	8		24	23	40										
3	9	12	25	24	41										
	10	13	26	25	42										
	11		27	26	43										
4	12	14	28	27	44										
5	13	15	29		45										
6	14	16	30												
	15	17	31												
7	16	18	32												

/S.P./ Examiner.Art Unit 1627	01/28/2014	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	27	
/SARAH PIHONAK/ Examiner.Art Unit 1627	01/28/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/13/2009	07/20/2010	03/08/2012	12/06/2012	01/28/2014				
1	1	✓	✓	✓	✓	=				
	2	✓	✓	✓	✓	-				
	3	✓	✓	✓	✓	-				
2	4	✓	✓	✓	✓	=				
	5	N	N	N	N	-				
	6	N	N	N	N	-				
	7	N	N	N	N	-				
	8	✓	-	-	-	-				
3	9	✓	✓	✓	✓	=				
	10	✓	-	-	-	-				
	11	✓	✓	✓	✓	-				
4	12	✓	✓	✓	✓	=				
5	13	✓	✓	✓	✓	=				
6	14	✓	✓	✓	✓	=				
	15	✓	-	-	-	-				
7	16	✓	✓	✓	✓	=				
	17	✓	-	-	-	-				
	18	✓	-	-	-	-				
	19	✓	✓	✓	✓	-				
8	20	✓	✓	✓	✓	=				
9	21	✓	✓	✓	✓	=				
10	22	✓	✓	✓	✓	=				
11	23	✓	✓	✓	✓	=				
	24	✓	✓	✓	✓	-				
12	25		✓	✓	✓	=				
13	26		✓	✓	✓	=				
	27			✓	✓	-				
14	28			✓	✓	=				
15	29			✓	✓	=				
16	30			✓	✓	=				
17	31			✓	✓	=				
18	32			✓	✓	=				
	33			✓	✓	-				
19	34			✓	✓	=				
	35			N	N	-				
	36			N	N	-				

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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CLAIM		DATE								
Final	Original	11/13/2009	07/20/2010	03/08/2012	12/06/2012	01/28/2014				
20	37				✓	=				
21	38					=				
22	39					=				
23	40					=				
24	41					=				
25	42					=				
26	43					=				
27	44					=				
	45					-				

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	"20040028741".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:16
L2	297	lurasidone or latuda	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:19
L3	22732	starch with (pregelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:19
L4	4808	starch with (pre-gelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:19
L5	167535	starch with (gelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:20
L6	176381	l3 or l4 or l5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:20
L7	143	l2 and l6	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:20
L8	10012	starch adj12 (pregelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:20
L9	3034	starch adj12 (pre-gelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:20
L10	91735	starch adj12 (gelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:20

EAST Search History (Prior Art)

L11	81	l2 and (l8 or l9 or l10)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:20
L12	1202	514/254.02.ccls.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:28
L13	991	544/368.ccls.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:29
L14	1914	l12 or l13	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:29
L15	477	l14 and (l8 or l9 or l10)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:29
L16	9371	starch adj6 (pregelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:31
L17	2950	starch adj6 (pre-gelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:31
L18	78571	starch adj6 (gelatin$6)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:31
L19	447	l14 and (l16 or l17 or l18)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:31
L20	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:37
L21	3436	dainippon.as.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:37
L22	11	l14 and l21	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:38
L23	11	l22 not l20	US-PGPUB; USPAT; USOCR	OR	OFF	2014/01/22 11:38

EAST Search History (Prior Art)

L24	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2014/01/22 11:41
S1	4	"2001076557".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2009/07/17 07:52
S2	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:53
S3	2622	pre-gelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S4	0	S2 and S3	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S5	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:54
S6	25	S2 and S5	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 12:55
S7	234938	oral and pharmaceutical	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S8	10067	S5 and S7	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S9	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:01
S10	446	S9 and oral	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:02

EAST Search History (Prior Art)

S11	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:17
S12	68	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S13	1	S11 and S12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S14	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S15	86	S11 and S14	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:18
S16	1916	(pregelatin$4 with starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 13:57
S17	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S18	86	S16 and S17	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:09
S19	1	"3607394".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2009/11/12 14:11
S20	67	(pregelatin$4 with starch) same (polymer with binder)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:29

EAST Search History (Prior Art)

S21	14534	pregelatin$4 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S22	745	S21 and (starch adj "1500")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:39
S23	47786	water adj solub$4 adj polymer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40
S24	43	S22 and S23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:40
S25	99	S21 and (PCS)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/12 14:42
S26	5	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2009/11/12 15:05
S27	4	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2009/11/12 15:07
S28	1803	starch adj "1500"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S29	1747	S28 and (**w**ater or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:14
S30	202	S28 with (water or moisture)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2009/11/13 14:15
S31	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2010/07/20 12:22
S32	4	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:23

EAST Search History (Prior Art)

S33	84	lurasidone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:24
S34	15801	pregelatin$5 with starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:25
S35	31	S33 and S34	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:25
S36	23548	accugel or absorbo or actobody or alphajel or allbond or alstar or amaizo or amalean or amerikor or amicoa or amidex or amigel or amilofax or amilys or amisol or amycol or amylex or amylogel or amylogum or amylomaize or amylon or amylose	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:27
S37	0	S33 and S36	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2010/07/20 12:28
S38	1	"4600579".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/11/02 11:19
S39	2	"20040028741".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2012/03/08 12:35
S40	1936	(corn adj starch) with (pregelatinized adj starch)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 13:13
S41	1138	(corn adj starch) adj5 (pregelatinized adj starch)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 13:13
S42	4	"2002053140".pn.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:12
S43	4	"2003066039".pn.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:13
S44	6	"2005009999".pn.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:15

EAST Search History (Prior Art)

S45	2389	((pregelatinize$1 or pregelatinise$1) adj4 starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:50
S46	16953	((improve$4 or increas$4) adj4 (solubility or soluble)).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:51
S47	41	S45 and S46	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/03/08 14:51
S48	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT	OR	OFF	2012/03/08 16:19
S49	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2012/03/08 16:19
S50	3215	dainippon.as.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:20
S51	232	((pregelatinize$1 or pregelatinise$1) with starch).ab.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:21
S52	1	S50 and S51	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:21
S53	1	S48 and S51	US-PGPUB; USPAT; USOCR	OR	OFF	2012/03/08 16:22
S54	22381	(pregelatin$6 or (pre-gelatin$6)) adj6 starch	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:31
S55	3343	((pregelatin$6 or (pre-gelatin$6)) adj6 starch).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:32
S56	942420	(solubility or dissolution or $4availability or soluble or $4available).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33
S57	1105	S55 and S56	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33

EAST Search History (Prior Art)

S58	195	lurasidone or latuda	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33
S59	3	S57 and S58	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:33
S60	1572986	(drug or pharmaceutical or medicine or medicament or active).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:34
S61	719	S57 and S60	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:35
S62	64608	(schizophren$2 or psychosis or psychotic or neurological or psychiatric or mental or cognit$3).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:40
S63	37	S61 and S62	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2012/11/26 10:40
S64	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:04
S65	6	((KAZUYUKI) near2 (FUJIHARA)).INV.	EPO; JPO; DERWENT	OR	OFF	2012/11/26 11:04
S66	3294	dainippon.as.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:05
S67	1	S55 and S66	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:05
S68	39	S54 and S66	US-PGPUB; USPAT; USOCR	OR	OFF	2012/11/26 11:05

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                 E STARCH,PREGELATINIZED/CN

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L4             1 S E64
L5          3627 S 9005-25-8/CRN
L6             0 S 9005-25-8D/RN
                 E 9005-25-8D/RN
                 E E75
L7             1 S E88
                 E PREGELATINIZED STARCH/CN
L8             0 S STARCH, PREGELATINIZED/CN
                 E STARCH, PREGELATINIZED/CN
                 E LURASIDONE/CN
L9             1 S E124
L10            3 S 367514-87-2/CRN

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L12        16134 S (?GELATIN?)(S) (?STARCH?)
                 E PHARMACEUTICAL TABLETS/CT
                 E E136+ALL/CT
L13        71281 S E155-E156,E162-E163,E165
L14        16134 S L11 OR L12
L15          171 S L9 OR L10
L16            2 S L14 AND L15
L17            1 S L16 NOT L1
L18         1280 S L13 AND L14
L19          385 S L2 AND L18
L20           36 S L19 AND (PY<=2006 OR AY<=2006 OR PRY<=2006)
L21           35 S L20 NOT L1
L22          267 S L18 AND (PY<=2006 OR PRY<=2006 OR AY<=2006)
L23          266 S L22 NOT L1
L24          231 S L23 NOT L21
L25           66 S (DISSOLUTION? OR DISSOLV? OR SOLUB? OR ?AVAILAB?) AND L24
L26          669 S L2 AND L14
L27          669 S (DISSOLUTION? OR DISSOLV? OR SOLUB? OR ?AVAILAB?) AND L26
L28          180 S L27 AND (PY<=2006 OR PRY<=2006 OR AY<=2006)
L29          144 S L28 NOT (L1 OR L21 OR L25)
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L1 STRUCTURE UPLOADED

L1 STRUCTURE UPLOADED

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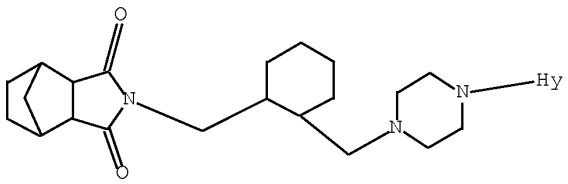
L1 STR



L2 2 S L1 SSS SAM
L3 82 S L1 SSS FULL
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SET EXPAND CONTINUOUS
E STARCH/CN
L4 1 S E15

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2014 ACS on STN
RN 9005-25-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN Starch (CA INDEX NAME)
OTHER NAMES:
CN α-Starch
CN 75A
CN 75A (polysaccharide)
CN A 1FB004215
CN Absorbo HP
CN AccuGel
CN Ace P 320
CN Actobody TP 2
CN ADM Clineo 716
CN Aeromyl 115
CN Agglofroid 009
CN Agglofroid 313E
CN Allbond 200
CN Alphajel KS 37
CN Alstar B
CN Alstar E
CN Alstar H
CN Amaizo 100
CN Amaizo 213
CN Amaizo 310
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CN Amalean I-A 2131
CN Amalean I-A 7081
CN Amerikor 818
CN Amicoa
CN Amidex 3001
CN Amidex 3005
CN Amidex 4001
CN Amido-STA 1500
CN Amidomax 4800
CN Amigel
CN Amigel 12014
CN Amigel 30076
CN Amijel VA 160
CN Amilofaks
CN Amilofax 00
CN Amilys 100
CN Amisol 3408
CN Amycol HF
CN Amycol K
CN Amycol W
CN Amylex 20/20
CN Amylogel
CN Amylogel 03001
CN Amylogel 03003
CN Amylogel HB 450
CN Amylogum
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DEF A high-polymeric carbohydrate material primarily composed of amylopectin and amylose. It is usually derived from cereal grains such as corn, wheat and sorghum, and from roots and tubers such as potatoes and tapioca. It includes starch which has been pregelatinized by heating in the presence of water.
DR 9057-05-0, 42616-76-2, 53112-52-0, 53262-79-6, 60496-95-9, 67674-80-0, 75138-75-9, 75398-82-2, 85746-25-4, 118550-61-1, 131800-97-0, 152987-55-8, 154636-77-8, 730985-55-4, 730985-56-5, 730985-57-6, 955949-61-8, 1374255-25-0
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration, Polyother, Polyother only
SR CA
LC STN Files: ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSNB, DDFU, DRUGU, EMBASE, IFIALL, IPA, MEDLINE, MSDS-OHS, NAPRALERT, PIRA, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

L5 0 S 9005-25-8D/RN
E 9005-25-8D/RN
E 9005-25-8D/CRN
L6 3627 S E38

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     FILE 'CAPLUS' ENTERED AT 09:28:34 ON 28 JAN 2014
L7          181 S L3
L8        24610 S L6
L9            3 S L7 AND L8

L9   ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2014 ACS on STN
AB    This invention relates to pharmaceutical compns. comprising one or more
      weakly basic antipsychotic drugs, and methods of making and using such
      compns.  Controlled release compns. comprise a plurality of controlled
      release particles comprising and acid core, a first coating of water
      insol. polymer, a second coating containing an antipsychotic drug and a
      third coating comprising a water insol. polymer.
ACCESSION NUMBER:         2011:880401  CAPLUS  Full-text
DOCUMENT NUMBER:          155:222666
TITLE:                    Controlled release pharmaceutical comprising
                          antipsychotic drugs
INVENTOR(S):              Venkatesh, Gopi M.; Lai, Jin-Wang; Papp, Michelle
PATENT ASSIGNEE(S):       Eurand, Inc., USA
SOURCE:                   PCT Int. Appl., 73pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND  DATE        APPLICATION NO.          DATE
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     WO 2011085188         A1   20110714    WO 2011-US20505          20110107
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CL, 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, PE,
             PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV,
             SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
ZW
         RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
             HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
             SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL,
             SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                    US 2010-61293067     P  20100107



L10       15990 S (STARCH?) (S) (?PREGELATIN? OR ?GELATIN?)
L11       18340 S (STARCH?) (L) (?PREGELATIN? OR ?GELATIN?)
L12        6365 S (STARCH?) (A) (?PREGELATIN? OR ?GELATIN?)
L13       15990 S (STARCH?) (XA) (?PREGELATIN? OR ?GELATIN?)
L14       18340 S L10 OR L11 OR L12 OR L13
L15           2 S L7 AND L14


L15  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2014 ACS on STN
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AB A preparation for oral administration comprises a pregelatinized starch comprising N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone hydrochloride) as an active ingredient; a water-soluble excipient; and a water-soluble polymeric binder, where the preparation exhibits an invariant level of elution behavior even when the content of its active ingredient is varied. For example, tablets were formulated containing lurasidone 80, mannitol 144, pregelatinized starch 80, croscarmellose sodium 4, hydroxypropyl Me cellulose 8, and Mg stearate 4 mg per tablet and film coated with a composition containing hydroxypropyl Me cellulose, titania, polyethylene glycol, and carnauba wax.

ACCESSION NUMBER: 2006:1252571 CAPLUS Full-text
DOCUMENT NUMBER: 146:13212
TITLE: Oral pharmaceutical compositions of lurasidone
INVENTOR(S): Fujihara, Kazuyuki
PATENT ASSIGNEE(S): Dainippon Sumitomo Pharma Co., Ltd., Japan
SOURCE: PCT Int. Appl., 42pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006126681	A1	20061130	WO 2006-JP310571	20060526
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2006250340	A1	20061130	AU 2006-250340	20060526
AU 2006250340	B2	20120209		
CA 2606510	A1	20061130	CA 2006-2606510	20060526
EP 1884242	A1	20080206	EP 2006-746900	20060526
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KR 2008012306	A	20080211	KR 2007-7027270	20060526
CN 101184489	A	20080521	CN 2006-80018223	20060526
CN 101184489	B	20110119		
RU 2398586	C2	20100910	RU 2007-148997	20060526
BR 2006011409	A2	20101123	BR 2006-11409	20060526
CN 102048734	A	20110511	CN 2010-10564784	20060526
CN 102048734	B	20131120		
JP 4733120	B2	20110727	JP 2007-517921	20060526
EP 2422783	A1	20120229	EP 2011-181100	20060526
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PT 1884242	E	20130521	PT 2006-746900		20060526
ES 2408687	T3	20130621	ES 2006-746900		20060526
KR 2013122019	A	20131106	KR 2013-7027051		20060526
TW 359020	B	20120301	TW 2006-121223		20060614
US 20090143404	A1	20090604	US 2007-919678		20071031
MX 2007014872	A	20080215	MX 2007-14872		20071123
IN 2007CN05369	A	20080125	IN 2007-CN5369		20071126
HK 1108379	A1	20130726	HK 2008-102367		20080303
JP 2011126915	A	20110630	JP 2011-61211		20110318
JP 5285105	B2	20130911			
PRIORITY APPLN. INFO.:			JP 2005-153508	A	20050526
			CN 2006-80018223	A3	20060526
			EP 2006-746900	A3	20060526
			JP 2007-517921	A3	20060526
			KR 2007-7027270	A3	20060526
			WO 2006-JP310571	W	20060526

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

IPCI A61K0031-496 [I]; A61K0009-20 [I]; A61K0047-10 [I]; A61K0047-26 [I]; A61K0047-38 [I]; C07D0417-12 [I]

IPCR A61K0031-496 [I]; A61K0009-20 [I]; A61K0047-10 [I]; A61K0047-26 [I]; A61K0047-38 [I]; C07D0417-12 [I]

CC 63-6 (Pharmaceuticals)

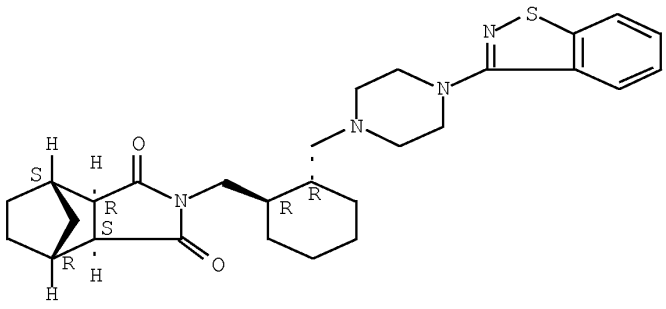
IT 63-42-3, Lactose 69-65-8, D-Mannitol 9005-25-8D, Starch, pregelatinized 367514-87-2, Lurasidone 367514-88-3, Lurasidone hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of lurasidone with improved dissoln. profile)

IT 367514-87-2, Lurasidone 367514-88-3, Lurasidone hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of lurasidone with improved dissoln. profile)

RN 367514-87-2 CAPLUS

CN 4,7-Methano-1H-isoindole-1,3(2H)-dione, 2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]methyl]cyclohexyl]methyl]hexahydro-, (3aR,4S,7R,7aS)- (CA INDEX NAME)

Absolute stereochemistry.

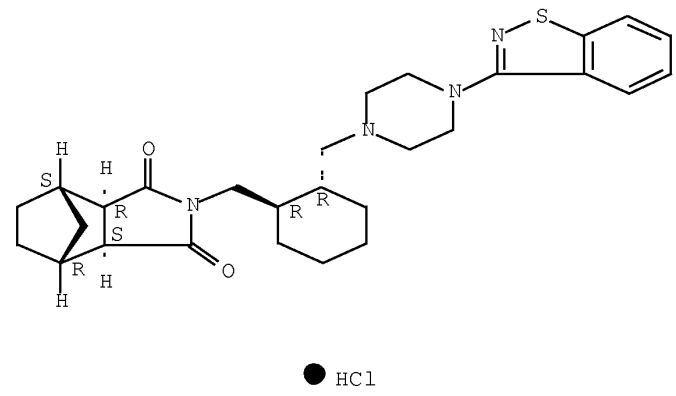


RN 367514-88-3 CAPLUS

CN 4,7-Methano-1H-isoindole-1,3(2H)-dione, 2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-

piperazinyl]methyl]cyclohexyl]methyl]hexahydro-, hydrochloride (1:1), (3aR,4S,7R,7aS)- (CA INDEX NAME)

Absolute stereochemistry.



● HCl

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11919678	FUJIHARA, KAZUYUKI
	Examiner	Art Unit
	SARAH PIHONAK	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	254.02	1/21/2014	S.P.
544	368	1/21/2014	S.P.

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search in EAST, PALM	11/12/2009	S.P.
Invention and claims search in EAST, STN	11/12/2009	S.P.
Inventor search in EAST, PALM	7/12/2010	S.P.
Invention and claims search in EAST, STN	7/12/2010	S.P.
invention and claims search updated in EAST, STN	3/8/2012	S.P.
updated inventor and assignee search in EAST, PALM	3/8/2012	S.P.
updated inventor and assignee search in EAST, PALM	11/26/2012	S.P.
updated invention and claims search in EAST, STN	11/26/2012	S.P.
STIC search	11/30/2012	S.P.
updated invention and claims search in STN, EAST	1/21/2014	S.P.
updated inventor and assignee search in EAST, PALM	1/21/2014	S.P.

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/S. P./ Examiner.Art Unit 1627	

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
514	254.02	1/21/2014	S.P.
544	368	1/21/2014	S.P.

/S. P./ Examiner.Art Unit 1627	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	11/919,678
				Filing Date	October 31, 2007
				First Named Inventor	Kazuyuki FUJIHARA
				Art Unit	1627
				Examiner Name	Sarah PIHONAK
Sheet	1	of	1	Attorney Docket Number	05273.0147-00000

U.S. PATENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Issue or Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-			
		US-			
		US-			

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[6]

NONPATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation[6]
/S.P./		Request for Invalidation from invalidity proceedings in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), August 5, 2012.	Yes
/S.P./		Bi Dianzhou, Pharmaceutics, Edition 4, Beijing: People's Medical Publishing House, February 2003.	Yes
/S.P./		"Application and Effect of Pregelatinized Starch in Tablets," Chinese Pharmaceutical Information, Vol.16, Issue 7, 2000, published in 2000	Yes
/S.P./		"Use of Pregelatinized Starch in Tablet Manufacturing," Chinese Pharmaceutical Journal, Vol. 29, Issue 4, April 1994, published in April 1994.	Yes
/S.P./		"Application of the Pregelatinized Starch in Capsules," Chinese Journal of Modern Applied Pharmacy, Vol. 8, Issue 1, February 1991, published in February 1991	Yes
/S.P./		"*In Vitro* Dissolution and Bioavailability of Acyclovir Capsules Formulated with Pregelatinized Starch," Chinese Journal of Pharmaceuticals, 1998, 29(5), published on May 20, 1998.	Yes
/S.P./		Dissolution of Drug Solid Preparation, "Factors Influencing Dissolution Rates," Wu Guangchen, Yue Zhiwei, People's Medical Publishing House, published in October 1994.	Yes
/S.P./		Reply Brief from invalidity proceedings in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), October 25, 2012.	Yes
/S.P./		Examination Decision on the Request for Invalidation in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), April 26, 2013.	Yes

Examiner Signature	/Sarah Pihonak/	Date Considered	01/22/2014

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P./

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22852 7590 02/03/2014
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	10/31/2007	Kazuyuki Fujihara	05273.0147-00000	6965

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	05/05/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-254020

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Finnegan, Henderson
2 Farabow, Garrett &
Dunner, LLP

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Dainippon Sumitomo Pharma Co., Ltd.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Osaka, Japan

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 06-0916 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature Charles E Van Horn Date April 9, 2014
Typed or printed name Charles E. Van Horn Registration No. 40,266

PATENT
Customer No. 22,582
Attorney Docket No. 05273.0147-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
	)
Kazuyuki FUJIHARA	) Group Art Unit: 1627
	)
Application No.: 11/919,678	) Examiner: Sarah Pihonak
	)
Filed: October 31, 2007	)
	) Confirmation No.: 6965
For: PHARMACEUTICAL COMPOSITION	)
	) VIA EFS-WEB

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

Applicant thanks the Examiner for the Notice of Allowance mailed February 3, 2014. Without withdrawing the allowed claims from issue, Applicant submits these comments for the record.

In the Notice of Allowance, the Examiner provided detailed remarks and a statement of reasons for allowance. Although Applicant agrees with the Examiner's ultimate conclusion that the claims are patentable, Applicant does not necessarily agree with each and every characterization and assertion contained in the Examiner's statement.

Please charge any fee due in connection with the filing of these Comments, to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: April 9, 2014

By: Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266
(202) 408-4000

Electronic Patent Application Fee Transmittal

Application Number:	11919678
Filing Date:	31-Oct-2007
Title of Invention:	PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Filer:	Charles E. Van Horn/Charlene Woods
Attorney Docket Number:	05273.0147-00000

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt

EFS ID:	18722092
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	22852
Filer:	Charles E. Van Horn/Charlene Woods
Filer Authorized By:	Charles E. Van Horn
Attorney Docket Number:	05273.0147-00000
Receipt Date:	09-APR-2014
Filing Date:	31-OCT-2007
Time Stamp:	20:52:32
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	8177
Deposit Account	060916
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	Issue_Fee.pdf	130914 390a0df43528d1628b6e791c0cbea154083fd7ff	no	1
Warnings:					
Information:					
2	Post Allowance Communication - Incoming	Comments_on-Statement_of_Reasons_for_Allowance.pdf	57653 dc69ecef8d5b5ec9d16ea70a7418e54a29ab1150	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30467 22d852b6eed7b6350812376487796a5802119479b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	219034	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Used in Lieu of PTO/SB/08A/B
(Based on PTO 01-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/919,678-Conf. #6965
Filing Date	October 31, 2007
First Named Inventor	Kazuyuki FUJIHARA
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	0020-5610PUS1

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO 02/24166 A1	03-28-02			Abs
	BB	WO 2004/078173 A1	~~10-12-1990~~	2004-09		Abs
	BC	JP-08-325146	12-10-1996			Abs

Change(s) applied to document,
/D.D./
3/7/2014

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Handbook of Pharmaceutical Excipients, 2nd edition, Vol. 491, The Pharmaceutical Press, 1994	

Examiner Signature	/Sarah Pihonak/	Date Considered	11/13/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Birch, Stewart, Kolasch & Birch, LLP

DRN/kpc

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.P./

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/919,678	05/20/2014	8729085	05273.0147-00000	6965

22852 7590 04/30/2014

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER
LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Kazuyuki Fujihara, Osaka-fu, JAPAN;

Customer Number 22,852
Attorney Docket No. 05273.0147

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Kazuyuki FUJIHARA	)	Group Art Unit: 1627
Application No.: 11/919,678	)	Examiner: Sarah Pihonak
U.S. Patent No: 8,729,085 B2	)	Confirmation No.: 6965
For: PHARMACEUTICAL COMPOSITION	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

FEE ADDRESS FOR MAINTENANCE FEE PURPOSES IN ACCORDANCE WITH 37 C.F.R. 1.363

In accordance with the provisions of 37 C.F.R. 1.363, the fee address set forth below is being supplied for purposes of receiving notices, receipts, and other correspondence relating to the payment of maintenance fees:

AOYAMA & PARTNERS
Osaka North P.O. Box 16
Osaka, 530-8691
JAPAN

Customer/Payor No.: 95780

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: 20 June 2014

By: Charles E Van Horn
Charles E. Van Horn
Reg. No. 40,266

Electronic Acknowledgement Receipt

EFS ID:	19368610
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	22852
Filer:	Charles E. Van Horn/Peter Nerenstone
Filer Authorized By:	Charles E. Van Horn
Attorney Docket Number:	05273.0147-00000
Receipt Date:	20-JUN-2014
Filing Date:	31-OCT-2007
Time Stamp:	16:09:01
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Maintenance Fee Address Change	MaintenanceFeeAddressChange.pdf	49124 12eeebdd69db3a60d47b6c42f408dc1e3f160b00	no	1

Warnings:	
Information:	

Total Files Size (in bytes):	49124

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Customer No. 22,852
Attorney Docket No. 05273.0147

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 8,729,085 B2	)	
	)	
Inventor: Kazuyuki FUJIHARA	)	Confirmation No.: 6965
	)	
Issue Date.: May 20, 2014	)	
	)	VIA EFS WEB
For: PHARMACEUTICAL COMPOSITION	)	
	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REQUEST FOR CERTIFICATE OF CORRECTION

Pursuant to 35 U.S.C. 254 and 37 C.F.R. 1.322, this is a request for the issuance of a Certificate of Correction in the above-identified patent. A copy of PTO Form 1050 is appended herewith. The complete Certificate of Correction involves one (1) page.

The mistakes identified in the attached form occurred through the fault of the Patent Office, as clearly disclosed by the records of the application which matured into this patent. Issuance of the Certificate of Correction containing the correction is earnestly requested.

If it should be determined that any of the mistakes resulted from an error made in good faith by the applicants, then, pursuant to 35 U.S.C. 255 and 37 C.F.R. 1.323, it is requested that a Certificate of Correction be issued correcting such mistakes. Under such circumstances, it is requested that the fee set forth in 37 C.F.R. 1.20(a) and any

additional fees needed be charged to our Deposit Account No. 06-0916, for which authorization is hereby given.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP

Dated: January 5, 2015

By: Charles E Van Horn

Charles E. Van Horn
Reg. No. 40,266

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. 8,729,085 B2

DATED: KAZUYUKI FUJIHARA

INVENTORS: PHARMACEUTICAL COMPOSITION

It is hereby certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 1, column 27, lines 14-17,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

In claim 10, column 27, line 57,
"50 by volume" should read --50% by volume--.

In claim 20, column 28, lines 33-36,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

In claim 26, column 29, lines 9-12,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

In claim 27, column 30, lines 5-8,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

MAILING ADDRESS OF SENDER

Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP
901 New York Avenue, NW
Washington, D.C. 20001-4413

Patent No. 8,729,085 B2

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Electronic Acknowledgement Receipt

EFS ID:	21132918
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	22852
Filer:	Ernest F. Chapman/veronica bayne
Filer Authorized By:	Ernest F. Chapman
Attorney Docket Number:	05273.0147-00000
Receipt Date:	06-JAN-2015
Filing Date:	31-OCT-2007
Time Stamp:	15:50:58
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	05273_0147_PTO_REQUEST_COC.pdf	124803 5fa270f4ff92fe38e57edf172d780e1ff1728436	no	3

Warnings:	
Information:	

Total Files Size (in bytes):	124803

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,729,085 B2
APPLICATION NO. : 11/919678
DATED : May 20, 2014
INVENTOR(S) : Fujihara

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE CLAIMS:

In claim 1, column 27, lines 14-17,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

In claim 10, column 27, line 57,
"50 by volume" should read --50% by volume--.

In claim 20, column 28, lines 33-36,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

In claim 26, column 29, lines 9-12,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

In claim 27, column 30, lines 5-8,
"N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4S)-2,3-bicyclo[2,2,1]heptanedicarboxylmide" should read
--N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide--.

Signed and Sealed this
Thirty-first Day of March, 2015

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5. If the Power of Attorney by Applicant form is not accompanied by this transmittal form or an equivalent, the Power of Attorney will not be recognized in the application.

Application Number	11/919,678
Patent Number	8,729,085
Filing Date	October 31, 2007
Issue Date	May 20, 2014
First Named Inventor	Kazuyuki FUJIHARA
Title	PHARMACEUTICAL COMPOSITION
Art Unit	1627
Examiner Name	PIHONAK, SARAH
Attorney Docket Number	472659US40PCT

SIGNATURE of Applicant or Patent Practitioner

Signature	/Yuki Onoe/	Date	07/21/16
Name	Yuki Onoe	Telephone	703-413-3000
Registration Number	68,563		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications.

■ *Total of 1 forms are submitted.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

Attorney Docket Number:	472659US40PCT

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with the Customer Number: 22850

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO), in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

■ The address associated with Customer Number: 22850

Assignee Name and Address:
Sumitomo Dainippon Pharma Co., Ltd.
6-8, Dosho-machi 2-chome, Chuo-ku,
Osaka-shi, Osaka 541-8524 Japan

A copy of this form, together with a statement under 37 CFR 3.73(c) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Hitoshi Fujita	Date	July 12, 2016
Name	Hitoshi FUJITA	Telephone	
Title	Director Intellectual Property		

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: SUMITOMO DAINIPPON PHARMA CO., LTD.

Application No./Patent No.: 8,729,085 Filed/Issue Date: May 20, 2014

Entitled: PHARMACEUTICAL COMPOSITION

SUMITOMO DAINIPPON PHARMA CO., LTD. (Name of Assignee) corporation (Type of Assignee, e.g., corporation, partnership, government agency, etc.)

States that it is:

1. ■ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest.

The extent (by, percentage) of its ownership interest is _____%

in the patent application/patent identified above by virtue of:

■ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Kazuyuki Fujihara To: Dainippon Sumitomo Pharma Co., Ltd.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 020124, Frame 0821, or for which a copy therefore is attached.

2. From: Dainippon Sumitomo Pharma Co., Ltd. To: SUMITOMO DAINIPPON PHARMA CO., LTD.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 033905, Frame 0778, or for which a copy therefore is attached.

3. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy therefore is attached.

■ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Yuki Onoe/ — Signature

07/21/16 — Date

Yuki Onoe — Printed or Typed Name - Attorney of Record

703-413-3000 — Telephone Number

68,563 — Registration Number

Electronic Acknowledgement Receipt

EFS ID:	26417678
Application Number:	11919678
International Application Number:	
Confirmation Number:	6965
Title of Invention:	PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Kazuyuki Fujihara
Customer Number:	22852
Filer:	Bradley Davis Lytle/Ellen Murabito
Filer Authorized By:	Bradley Davis Lytle
Attorney Docket Number:	05273.0147-00000
Receipt Date:	21-JUL-2016
Filing Date:	31-OCT-2007
Time Stamp:	14:59:26
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		472659US-F.pdf	1031162 fbe82fb49ecf0465aec1f567764aa42bf2887 3ad	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	2
	Assignee showing of ownership per 37 CFR 3.73	3	3
Warnings:			
Information:			
	Total Files Size (in bytes):	1031162	

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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/919,678	10/31/2007	Kazuyuki Fujihara	472659US40PCT

CONFIRMATION NO. 6965

22850
OBLON, MCCLELLAND, MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

POA ACCEPTANCE LETTER

OC000000084622229

Date Mailed: 07/27/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/21/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/rmturner myles/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/919,678	10/31/2007	Kazuyuki Fujihara	472659US40PCT

CONFIRMATION NO. 6965

22852
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

POWER OF ATTORNEY NOTICE

OC000000084622227

Date Mailed: 07/27/2016

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/21/2016.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/rmturner myles/