PATENT APPLICATION SERIAL NO. 10/031464

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

01/29/2002 SNAJARRO 00000015 10031464

01 FC:970 890.00 DP
02 FC:966 108.00 DP

PTO-1556
(5/87)

*U.S. GPO: 2000-468-987/39595

Barbara Campbell
National Stage Processing
(703) 305-3331

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number
10/031464

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	26 minus 20=	* 6
INDEPENDENT CLAIMS	1 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	89
X$ 9=		OR	X$18=	108
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
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. 10/031464

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2						
3		1				
4		1				
5		1				
6		1				
7		1				
8		1				
9		1				
10		1				
11		1				
12		1				
13		1				
14		1				
15		1				
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19		1				
20		1				
21		1				
22		1				
23		1				
24		1				
25		1				
26		1				
27		1	Canceled			
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50						
TOTAL IND.		⬇	1	⬇		⬇
TOTAL DEP.		⬅	25	⬅		⬅
TOTAL CLAIMS			26			

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
53						
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97						
98						
99						
100						
TOTAL IND.		⬇		⬇		⬇
TOTAL DEP.		⬅		⬅		⬅
TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS

Barbara Campbell
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FORM PTO-1360 (REV. 3-78)

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U.S.DEPARTMENT OF COMMERCE
Patent and Trademark Office

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 March 2001 (30.03.01)	
International application No. PCT/US00/11130	**Applicant's or agent's file reference** 29342/36230
International filing date (day/month/year) 26 April 2000 (26.04.00)	**Priority date** (day/month/year) 03 August 1999 (03.08.99)
Applicant OREN, Peter, L. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

05 February 2001 (05.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Marie-José Devillard
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992) US0011130

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
MARSHALL O'TOOLE GERSTEIN,
MURRAY & BORUN
Attn. NAPOLI,J
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
UNITED STATES OF AMERICA

	Date of mailing *(day/month/year)* 07/09/2000
Applicant's or agent's file reference 29342/36230	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 00/ 11130	International filing date *(day/month/year)* 26/04/2000
Applicant LILLY ICOS LLC et al.	DOCKETED: 11/7/00

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

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

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

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

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

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

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

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

4. **Further action(s):** The applicant is reminded of the following:

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

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

DOCKETED

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Catherine Humbert

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

When?

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

Where not to file the amendments?

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

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

How?

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

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

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

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

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

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

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

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

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

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

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

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

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

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

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

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NAPOLI, J., J.
MARSHALL O'TOOLE GERSTEIN,
MURRAY & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
ETATS-UNIS D'AMERIQUE

PCT

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

Date of mailing *(day/month/year)*	05.12.2001
Applicant's or agent's file reference 29342/36230	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/11130	26/04/2000	03/08/1999

Applicant
LILLY ICOS LLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

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

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

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

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Senkel, H Tel.+49 89 2399-8071

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
29342/36230		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/11130	26/04/2000	03/08/1999
International Patent Classification (IPC) or national classification and IPC A61K31/495		
Applicant LILLY ICOS LLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/02/2001	05.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Blott, C Telephone No. +49 89 2399 7538

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/11130

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-28 as originally filed

Claims, No.:

1-27 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

☐ the entire international application.

☒ claims Nos. 26,27.

because:

☒ the said international application, or the said claims Nos. 26 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

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

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

☒ no international search report has been established for the said claims Nos. 27 (incomplete).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,7,10-11,13,17-25
	No:	Claims	1-4,6,8-9,12,14-16,26-27
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-25,27

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

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

SECTION III

1. The IPEA will only formulate an assessment of novelty, inventive step and industrial applicability for the present claims for which an International Search Report has been drawn up, i.e. claims 1-26 (complete) and claim 27 (incomplete) (Rule 66.1(e) PCT)(cf. form PCT/ISA/210, box I.2).

2. Claim 26 relates to a subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Art. 34(4)(a)(i) PCT).

SECTION V

3. a) The following documents, which were cited in the International Search Report, are referred to in this report; the numbering will be adhered to in the rest of the procedure:

   D1: WO 97 03675 cited in the application
   D2: WO 96 38131 cited in the application
   D3: WO 98 23270

   b) D1 refers to the use of cGMP-phosphodiesterase inhibitors such as the compound mentioned in present claim 1 (=compound A), for the treatment of erectile dysfunction (cf. page 1, lines 1-6 and claims 1, 2). On page 13, D1 discloses tablets comprising:

-compound A	50 mg (10% w/w)
-polyvinyl pyrrolidone (PVP)	150 mg (30% w/w)
-polyethylene glycol (PEG)	50 mg (10% w/w)
-polysorbate 80	10 mg (2% w/w)
-magnesium stearate	2,5 mg (0,5% w/w)
-croscarmellose sodium	25 mg (5% w/w)
-colloidal silicon dioxide	2,5 mg (0,5% w/w)
-microcrystalline cellulose	210 mg (42% w/w)

   The compositions of D1 may also be administered in the form of capsules or ovules (cf. page 5, line 20 and pages 15-16).

   c) D2 is a patent application of the same applicant as D1. D2 discloses pharmaceutical formulations comprising a co-precipitate of compound A with

hydroxypropyl methyl cellulose phthalate (cf. examples). D2 does not disclose formulations comprising compound A as a free drug, provided that compounds comprised in a co-precipitate do not fall within the definition of the term "free drug" (cf. description page 5, lines 24-27 and section VIII 7.).

d) D3 refers to pharmaceutical formulations for oral administration of certain 3,4-diarylchromans in combinations with a hydrophilic binder and a water-soluble diluent (cf. page 1, lines 1-12). D3 does not refer to pharmaceutical formulations comprising compound A.

4. Novelty

a) D1 anticipates the subject-matter of present claim 1, since it discloses (cf. item 3.b)) pharmaceutical formulations comprising the active compound of claim 1 as a free drug, PEG, which may be considered a water-soluble diluent, magnesium stearate and colloidal silicon dioxide, which are lubricants, PVP=povidone, which is a hydrophilic binder, croscarmellose sodium, which is a disintegrant, polysorbate 80, which is a wetting agent and microcrystalline cellulose.

The subject-matter of claim 1 therefore lacks novelty over D1 (Art. 33(2) PCT).

b) Item a) also applies to dependent claims 2-4, 6, 8-9, 12, 14-16 as well as to claims 26-27.

c) None of the above-cited documents discloses nor anticipates the subject-matter of claims 5, 7, 10-11, 13, 17-25. The subject-matter of said claims therefore is new over the cited prior art documents (Art. 33(2) PCT).

5. Inventive step

Dependent claims 5, 7, 10-11, 13, 17-25 do not seem to contain any technical feature which is not easily derivable from D1, the closest prior art document, or which is not a matter of routine for the skilled person. The subject-matter of said claims therefore appears to lack an inventive step, especially since the Applicant did not provide evidence for the claimed effect, i.e. enhanced dosage uniformity, stability and bioavailability (cf. description page 7, lines 21-28) (Art. 33(3) PCT).

6. Industrial applicability

For the assessment of the present claim 26 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII

7. The term "...free drug..." used in claim 1 and in the description is unclear, especially since salts and solvates of the active compound also seem to fall within said definition (cf. page 4, lines 1-3 and page 5, lines 24-27) (Art. 6 PCT).

8. The term "about" in relation to a range used in claims 4-5, 8, 10, 12-14, 19-25 and in the description is vague and unclear (Art. 6 PCT).

9. Claim 16 erroneously refers back to claim 1. Claim 16 is dependent on claim 3 and should therefore contain, if possible at the beginning, a reference to this claim (Rule 6.4(a) PCT).

10. Claims 23 and 24 comprise all the features of claim 22 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4(a) PCT).

11. It seems that the following features are not referred to in the description. The claims are therefore not supported by the description as required by Art. 6 PCT:
-claims 7, 9, 11, 15, 16: "...mixtures..."
-claims 13, 20: "...5%..."
-claim 19: "...formulation comprising: (a)...(b)...(e) ...10% by weight croscarmellose sodium..."
-claims 22-24: "... a tablet comprising ...1 to about 20 mg (5 to about 15 mg) (5mg or about 10 mg)..."
-claim 25: "...about 1 to about 20 mg per capsule..."

#3

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/031,464	Peter L. Oren	29342/36230A

INTERNATIONAL APPLICATION NO.	
PCT/US00/11130	
I.A. FILING DATE	PRIORITY DATE
04/26/2000	08/03/1999

04743
MARSHALL, GERSTEIN & BORUN
6300 SEARS TOWER
233 SOUTH WACKER
CHICAGO, IL 60606-6357

CONFIRMATION NO. 6930

371 FORMALITIES LETTER

OC000000007803217

Date Mailed: 04/08/2002

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as an Elected Office (37 CFR 1.495):

- U.S. Basic National Fees
- Priority Document
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Preliminary Amendments

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date.

- **$130** Surcharge for providing the oath or declaration later than the appropriate 30 months months from the priority date (37 CFR 1.492(e)) is required.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTH FROM THE DATE OF THIS NOTICE OR BY 22 or 32 MONTHS (where 37 CFR 1.495 applies) FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

SUMMARY OF FEES DUE:

Total additional fees required for this application is **$130** for a Large Entity:

- **$130** Late oath or declaration Surcharge.

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)

*A copy of this notice **MUST** be returned with the response.*

BARBARA A CAMPBELL

Telephone: (703) 305-3631

PART 2 - OFFICE COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/031,464	PCT/US00/11130	29342/36230A

FORM PCT/DO/EO/905 (371 Formalities Notice)

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

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

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
29342/36230A	10/031464

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/11130	26 April 2000	03 August 1999

TITLE OF INVENTION

BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

APPLICANT(S) FOR DO/EO/US

OREN, Peter L.; ANDERSON, Neil R.; KRAL, Martha A.

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

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ 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. ☐ 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. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ 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. ☐ 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. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Return receipt postcard

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/031464	PCT/US00/11130	29342/36230A

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	26 - 20 =	6	x $18.00	$108.00	
Independent claims	1 - 3 =	0	x $84.00	$0.00	
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00	

TOTAL OF ABOVE CALCULATIONS =	$998.00	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	$0.00	
SUBTOTAL =	$998.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	$0.00	
TOTAL NATIONAL FEE =	$998.00	
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) **(check if applicable).** ☐	$0.00	
TOTAL FEES ENCLOSED =	$998.00	
Amount to be: refunded	$	
charged	$	

a. ☒ A check in the amount of **$998.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **13-2855** A duplicate copy of this sheet is enclosed.

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.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 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 application to pending status.

SEND ALL CORRESPONDENCE TO:

NAPOLI, James J.
Customer No. 04743
Marshall, Gerstein & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
United States of America

James J. Napoli
SIGNATURE

James J. Napoli
NAME

32,361
REGISTRATION NUMBER

17 January 2002
DATE

PATENT APPLICATION #2/a

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants: **PETER L. OREN ET AL.** U.S. National Phase of International Application No. PCT/US00/11130 filed under 35 U.S.C. §371 International Filing Date: 26 April 2000 Filed: Herewith For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS** Group Art Unit: Unknown Examiner: Unknown Attorney Docket No. 29342/36230A	"EXPRESS MAIL" mailing label No. **EK657815976US** Date of Deposit: **January 17, 2002** I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Commissioner of Patents, Washington, D.C. 20231. Richard Zimmermann

PRELIMINARY AMENDMENT ACCOMPANYING NEW APPLICATION TRANSMITTAL

Box PCT
Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified application filed under 35 U.S.C. §371 as follows:

IN THE SPECIFICATION:

Page 1, after the title, please delete the CROSS-REFERENCE TO RELATED APPLICATION in its entirety and insert therefor:

--**CROSS-REFERENCE TO RELATED APPLICATIONS**

This is the U.S. national phase application of International Application No. PCT/US00/11130, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/146,924, filed August 3, 1999.--

IN THE CLAIMS:

Cancel claim 27.

REMARKS

Claims 1-27 are pending in the application. Claim 27 has been cancelled by this amendment. Therefore, claims 1-26 are at issue.

The amendments are described in more detail below. Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the specification and claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

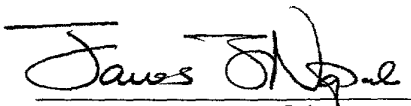
This preliminary amendment adds no new matter. The specification has been amended to insert a new cross reference to related applications. The claims have been amended to conform the claims to U.S. practice.

It is submitted that this amendment should be entered and that the claims are in proper form for examination. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
January 17, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE
(U.S. National Stage of PCT/US00/11130
filed January 17, 2002)

IN THE SPECIFICATION:

The following cross-reference to related application has been inserted into the specification:

CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11130, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/146,924, filed August 3, 1999.

IN THE CLAIMS:

Claim 27 has been cancelled without prejudice.

β-CARBOLINE PHARMACEUTICAL COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of provisional U.S. Patent Application Serial No. 60/146,924, filed August 3, 1999.

FIELD OF THE INVENTION

This invention relates to the fields of pharmaceutical and organic chemistry involving β-carboline compounds which are useful in the treatment of the various medical indications where inhibition of type 5 cGMP-specific phosphodiesterase is desired. More particularly, β-carboline compounds are formulated in a manner providing uniform potency, and desirable stability and bioavailability characteristics.

BACKGROUND OF THE INVENTION

The biochemical, physiological, and clinical effects of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE) inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP hydrolyzing enzyme in vascular smooth muscle, and its expression in penile corpus cavernosum has been reported (A. Taher et al., *J. Urol.*, *149*, pp. 285A (1993)).

Thus, PDE5 is an attractive target in the treatment of sexual dysfunction (K.J. Murray, *DN&P 6(3)*, pp. 150-56 (1993)).

Daugan U.S. Patent No. 5,859,006 discloses a class of β-carbolines, and pharmaceutical compositions thereof, which are useful in the treatment of conditions wherein inhibition of PDE5 is desired. Also, see PCT publication WO 97/03675 disclosing the use of such β-carbolines for the treatment of sexual dysfunction.

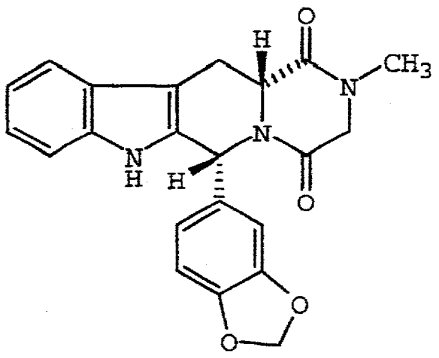
The poor solubility of many β-carbolines useful as PDE5 inhibitors has prompted the development of coprecipitate preparations, as disclosed in Butler U.S. Patent No. 5,985,326. Briefly described, coprecipitates of β-carbolines with a polymer, e.g., hydroxypropyl methylcellulose phthalate, were prepared, then milled, mixed with excipients, and compressed into tablets for oral administration. However, studies revealed some difficulties in generating precisely reproducible lots of coprecipitate product, thereby making the use of coprecipitates less than ideal for pharmaceutical formulations.

In addition, clinical studies involving administration of tablets containing such a coprecipitate preliminarily revealed that maximum blood concentration of the β-carboline is achieved in 3 to 4 hours, with the average time for onset of a therapeutic effect as yet not precisely determined. When used for the treatment of sexual dysfunction, such as male erectile dysfunction or female arousal disorder, a more rapid attainment of maximum blood concentration, along with a greater prospect for

rapid onset of therapeutic effect, is desired by patients, who prefer more immediate effects. Accordingly, there is a continuing need in the art for oral dosage forms of β-carbolines, and pharmaceutical compositions thereof, useful in the treatment of conditions where inhibition of PDE5 is beneficial.

SUMMARY OF THE INVENTION

This invention provides pharmaceutical formulations comprising a compound of structural formula (I):



(I)

named (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, and alternatively named (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione,

and pharmaceutically acceptable salts and solvates thereof, wherein the compound preferably is provided as a free drug,

in admixture with a diluent, a lubricant, a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof, a disintegrant selected from the group consisting of crospovidone, croscarmellose sodium, and a mixture thereof, and, optionally, microcrystalline cellulose and/or a wetting agent. Optionally, the formulation additionally comprises a second diluent.

A most preferred pharmaceutical formulation of the present invention comprises: (a) about 1 to about 5, and more preferably about 2 to about 4, weight percent of the compound of structural formula (I), provided as free drug; (b) about 50 to about 85 weight percent, and preferably about 50 to about 75 percent, lactose; (c) about 0.25 to about 2 weight percent magnesium stearate; (d) about 1 to about 5 weight percent hydroxypropylcellulose; (e) about 3 to about 15 weight percent croscarmellose sodium; (f) 0 to about 40 weight percent microcrystalline cellulose; and (g) 0 to about 5 weight percent sodium lauryl sulfate.

The present invention further relates to the use of such formulations for treatment of sexual dysfunction, e.g., male erectile dysfunction and female arousal disorder. The formulations can be administered orally as a compressed tablet or as dry, free-flowing particles encapsulated in a hard shell, for example, a gelatin shell.

DETAILED DESCRIPTION OF THE INVENTION

For purposes of the invention disclosed and claimed herein, the following terms and abbreviations have the following meanings.

The term "treatment" is defined to include preventing, lowering, stopping, or reversing the progression or severity of a condition or symptom being treated. As such, the present invention includes both medical therapeutic and/or prophylactic administration, as appropriate.

The term "effective amount" is an amount of a pharmaceutical formulation that is effective in treating the desired condition or symptom. An effective amount of the compound of structural formula (I) to treat sexual dysfunction in a male is an amount sufficient to provide and sustain an erection capable of penetrating his partner. An effective amount of the compound of structural formula (I) to treat female sexual dysfunction, particularly female arousal disorder, is an amount sufficient to enhance the patient's ability to achieve or sustain an aroused state.

The term "free drug" refers to solid particles consisting essentially of the compound of structural formula (I), as opposed to the compound intimately embedded in a polymeric coprecipitate.

The term "lubricant" refers to pharmaceutically acceptable agents that are commonly used in the art as lubricants or glidants in the preparation of solid pharmaceutical formulations. Representative lubricants include, but are not limited to, agents such as talc, magnesium stearate, calcium

stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, and hydrogenated vegetable oils. Preferably, the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, and stearic acid. Most preferably, the lubricant is magnesium stearate.

The term "solvate" refers one or more molecules of a solute associated with a molecule of a compound, such as the compound of structural formula (I) associated with a molecule of water or acetic acid.

The term "solid oral dosage form" is used in a general sense to refer to solid pharmaceutical products administered orally. Solid oral dosage forms are recognized by those skilled in the art to include such forms as tablets and capsules, for example.

The term "water-soluble diluent" refers to compounds typically used in the formulation of pharmaceuticals to impart bulk for the manufacture of a tablet of practical size. Water-soluble diluents include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), and cyclodextrins.

The term "wetting agent" refers to anionic, cationic, and nonionic surfactants. Nonlimiting, representative wetting agents include sodium lauryl sulfate, docusate sodium (i.e., bis(2-ethyl-

hexyl)sodium sulfosuccinate), ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides and ethoxylated derivatives thereof, and diglycerides and ethoxylated derivatives thereof. Preferably the surfactant is sodium lauryl sulfate or a polyoxyethylene sorbitan fatty acid ester, particularly polysorbate 80.

The nomenclature describing particle size is commonly referred to herein as the "d90." A d90 of 40 means that at least 90% of the particles have a particle size less than 40 microns.

As previously stated, the present invention provides pharmaceutical formulations containing the compound of structural formula (I), as disclosed in Daugan U.S. Patent No. 5,859,006, and pharmaceutically acceptable solvates thereof. A preferred solvent suitable to prepare the compound of structural formula (I) includes acetic acid.

Applicants have found that dosage uniformity, stability, and bioavailability are enhanced by formulating (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (i.e., the compound of structural formula (I), also referred to herein as Compound A), as the active compound with a particular combination of pharmaceutical excipients. The formulations of present invention comprise mixtures of the active compound with a water-soluble diluent, a lubricant, a hydrophilic binder, croscarmellose sodium or crospovidone as a disintegrant,

and, optionally, microcrystalline cellulose and/or a wetting agent.

The total amount of active Compound A in the pharmaceutical formulations is about 0.1% to about 45%, preferably about 0.5% to about 10%, by weight of the formulation. In more preferred embodiments, the active compound is present in an amount of about 1% to about 4%, and most preferably, about 2% to about 4%, by weight of the formulation. The compound of structural formula (I) can be made according to established procedures, such as those disclosed in Daugan U.S. Patent No. 5,859,006, incorporated herein by reference.

The particle size of the active compound also has been found to enhance the bioavailability and handling of the present formulations. Thus, the particle size of the compound of structural formula (I) prior to formulation is controlled by milling the raw compound (as a crystal, amorphous precipitate, or mixture thereof) such that at least 90% of the particles have a particle size of less than about 40 microns (d90=40), and preferably less than about 30 microns. More preferably, at least 90% of the particles have a particle size of less than about 25 microns, still more preferably, less than about 15 microns, and most preferably, less than about 10 microns.

Methods for determining the size of particles are well known in the art. The following nonlimiting method disclosed in U.S. Patent No. 4,605,517, incorporated herein by reference, can be employed. In particular, the laser scattering particle size distribution analysis is effected on a

small sample of the reduced material which is suspended in approximately 180 ml of dispersant solution. The sample is added to the dispersant until an acceptable level of laser light obscuration is achieved, at which point the particle size distribution is measured. Prior to sample suspension, a dispersant solution is prepared by preparing a solution of 0.1% SPAN 80 (sorbitan oleate) in cyclohexane which is presaturated with the compound. The dispersant solution is filtered through a 0.2 micron microporous membrane filter to provide the necessary particle-free suspending dispersant. Triplicate measurements are effected as a minimum (a) to produce more reliable measurements, and (b) to check the equivalent sampling of the suspended material. The results are automatically recorded and displayed graphically to give a cumulative % undersize vs. diameter, and a frequency percentage vs. diameter for the sample. From this data, the median equivalent spherical volume diameter value and d90 are derived (90% undersize value) together with the standard deviation of the distribution calculated as above.

A water-soluble diluent is present in the formulation in an amount sufficient to provide adequate bulk to the formulation, and to effect tablet manufacture. A preferred water-soluble diluent is lactose, present in an amount of about 50% to about 85%, and preferably, about 50% to about 75%, by weight.

A hydrophilic binder is provided in an amount sufficient to act as an adhesive to hold Compound A and excipients together in a tablet. A

hydrophilic binder also is present in a powder formulation introduced into a hard gelatin shell. In dry powder formulations, the hydrophilic binder facilitates powder manufacture and handling, and enhances stability of the active compound.

A preferred hydrophilic binder is a cellulose derivative, including, for example, hydroxypropylcellulose and hydroxypropyl methylcellulose. Other hydrophilic cellulose derivatives include, but are not limited to, hydroxyethylcellulose and hydroxybutyl methylcellulose. Another nonlimiting hydrophilic binder is povidone. Preferably, the amount of hydrophilic binder present in the formulation is about 1% to about 5%, by weight of the formulation.

While binders such as povidone provide suitable adhesive characteristics, it has been found that the binder is important with respect to the stability of the β-carboline compound. Hydroxypropylcellulose and hydroxypropyl methylcellulose offer acceptable adhesion, while avoiding the oxidative instability attributed to povidone, and thus are preferred binders.

The croscarmellose sodium and crospovidone promote disintegration of the formulation, and especially a tablet dosage form, after administration and upon contact with water. Croscarmellose sodium and crospovidone are particularly advantageous when used in an amount of about 3% to about 15%, and especially about 3% to about 10%, by weight of the formulation. Croscarmellose sodium, also known as carboxymethylcellulose sodium crosslinked,

is the preferred disintegrant. Crospovidone is crosslinked povidone.

A lubricant is provided in an amount sufficient to reduce die wall friction during compression of the formulation into tablets. Preferably, the lubricant is magnesium stearate, present in an amount of about 0.25% to about 2.0%, by weight of the formulation. A lubricant also facilitates handling of the dry powder form of the formulation.

Microcrystalline cellulose is present at 0 to about 40% by weight in the present compositions. Microcrystalline cellulose can serve multiple functions in the formulation, e.g., a disintegrant and/or a second diluent in addition to the water-soluble diluent.

If desired, wetting agents are provided in an amount sufficient to decrease interfacial tension between drug particles and the dissolving medium (e.g., gastric fluids), and thereby enhance drug dissolution and absorption. Preferably, the surfactant is sodium lauryl sulfate or a polyoxyethylene sorbitan fatty acid ester, particularly polysorbate 80, in an amount of 0% to about 5%, and preferably about 0.1% to about 5%, by weight of the formulation.

Additional optional ingredients, such as coloring or flavoring agents, can be incorporated into the formulation in an amount sufficient to perform their intended function without adversely affecting either the powder formulation or tablets manufactured using the formulation.

In preferred embodiments, the relative percentage of formulation components (by weight) is as follows:

	Quantity (% by weight)
Compound of Structural Formula (I)	1 to 4
Lactose (diluent)	50 to 85
Hydrophilic Binder	1 to 5
Croscarmellose Sodium (disintegrant)	3 to 15
Sodium Lauryl Sulfate (wetting agent)	0 to 5
Microcrystalline Cellulose (diluent/disintegrant)	0 to 40
Magnesium Stearate (lubricant)	0.25 to 2

The formulations of the present invention can be prepared by a variety of techniques recognized in the art. Such techniques include, for example, wet granulation followed by drying, milling and compression into tablets with or without film coating, dry granulation followed by milling, compression into tablets with or without film coating, dry blending followed by compression into tablets, with or with film coating, molded tablets, wet granulation, dried and filled into gelatin capsules, dry blend filled into gelatin capsules, or suspension or solution filled into gelatin capsules. Generally, the compositions have identifying marks which are debossed or imprinted on the surface.

In addition to improved dissolution and *in vivo* absorption, another important physical property is stability. The present invention provides formu-

lations with improved stability over prior formulations.

The specific dose of Compound A administered according to the present invention is determined by the particular circumstances surrounding the case including, for example, the route of administration, the dosage form, the condition of the patient, and the pathological condition being treated. A typical daily dose contains a dosage level of about 1 to about 20 mg/day of the compound of structural formula (I). Preferred daily doses generally are about 1 to about 10 mg/day, particularly about 5 mg or about 10 mg tablets or capsules, administered once per day. The most preferred dosage form is a tablet. Multiple doses can be taken to achieve a total dose of up to 20 mg/day of the compound of structural formula (I). The selection of dose level is decided by the attending physician.

One useful dosage form is a hard capsule comprising a powdered form of the formulation in a hard, soluble shell. In accordance with the present invention, the hard capsules are a solid dosage form in which dry, free-flowing particles of the drug formulation are filled in a hard container or shell comprising a gelatin, a starch, or other capsule materials well known to persons skilled in the art. Gelatin possesses unique properties which make gelatin the primary material for the manufacture of hard capsule shells. Another example of a useful capsule material is potato starch.

Hard capsules provide some advantages over other solid dosage forms, such as tablets. For

example, many patients prefer capsules because capsules are easier to swallow. Thus, capsule forms of a drug often are made available in addition to tablet forms.

A hard capsule has a hard shell completely surrounding the dry formulation. Typically, the dry drug formulation is added to a first section of the capsule, then a second section of the capsule is slipped over an open end of the first section to surround the drug formulation. The size and shape of the hard shell can vary, but typically is cylindrical with rounded ends. The size of the capsule is related to the dose level of the drug encapsulated by the shell, and to the particular drug formulation.

A hard capsule oral dosage form typically is prepared such that the shell ruptures or dissolves to release the enclosed drug formulation within five to ten minutes after ingestion. Manufacture of the hard shell, and the capsules, is performed in accordance with methods well known in the art.

The following formulation examples are illustrative only, and are not intended to limit the scope of the present invention. In particular, the following examples are directed to tablets, but the identical formulations, in a dry free-flowing particulate or powder form, can be used in a hard capsule.

EXAMPLE 1

Lot 1 of Compound A was made using a 12 inch pancake style jet mill fed at a rate of 28 to 30 kg/hour with sufficient grind pressure to produce material having a d90 of 4 microns.

The following formula was used to prepare the finished dosage form, i.e., a tablet providing 10.0 mg of Compound A from Lot 1 material.

Ingredient	Quantity (mg)
Granulation	
Compound A (d90 of 4)	10.0
Lactose Monohydrate	153.8
Lactose Monohydrate (spray dried)	25.0
Hydroxypropyl Cellulose	4.0
Croscarmellose Sodium	9.0
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.7
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.5
Croscarmellose Sodium	7.0
Magnesium Stearate (vegetable)	1.25
Total	250 mg

Purified Water, USP was used in the manufacture of the tablets. The water was removed during processing, and minimal levels remained in the finished product.

The tablets were manufactured using a wet granulation process. A step by step description of the process follows: Compound A and excipients were

security sieved. The selective PDE5 inhibitor (i.e., Compound A) was dry blended with lactose monohydrate (spray dried), hydroxypropyl cellulose, croscarmellulose sodium, and lactose monohydrate. The resulting powder blend was granulated with an aqueous solution of hydroxypropyl cellulose and sodium lauryl sulfate using a Powrex or other suitable high shear granulator. Additional water can be added to reach the desired endpoint. A mill can be used to delump the wet granulation and facilitate drying. The wet granulation was dried using either a fluid bed dryer or a drying oven. After the material was dried, it can be sized to eliminate large agglomerates.

Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate were security sieved and added to the dry sized granules. These excipients and the dry granulation were mixed until uniform, using a tumble bin, ribbon mixer, or other suitable mixing equipment. The mixing process can be separated into two phases: (a) the microcrystalline cellulose, croscarmellose sodium and the dried granulation are added to the mixer and blended, followed by (b) the addition of the magnesium stearate to this granulation and a second mixing phase.

The mixed granulation then was compressed into tablets using a rotary compression machine. The core tablets, if desired, can be film coated with an aqueous suspension of the appropriate color mixture in a coating pan (e.g., Accela Cota). The coated tablets can be lightly dusted with talc to improve tablet handling characteristics.

The tablets can be filled into plastic containers (30 tablets/container) and accompanied by a package insert describing the safety and efficacy of the compound.

EXAMPLE 2

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 5 mg of Compound A of Lot 1.

Ingredient	Quantity (mg)
Granulation	
Compound A (d90 of 4)	5.00
Lactose Monohydrate	109.655
Lactose Monohydrate (spray dried)	17.50
Hydroxypropyl Cellulose	2.80
Croscarmellose Sodium	6.30
Hydroxypropyl Cellulose (EF)	1.225
Sodium Lauryl Sulfate	0.49
Outside Powders	
Microcrystalline Cellulose (Granular-102)	26.25
Croscarmellose Sodium	4.90
Magnesium Stearate (vegetable)	0.88
Total	175 mg

EXAMPLE 3

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 2.5 mg of Compound A.

Ingredient	Quantity (mg)
Granulation	
Compound A	2.50
Lactose Monohydrate	79.395
Lactose Monohydrate (spray dried)	12.50
Hydroxypropyl Cellulose	2.00
Croscarmellose Sodium	4.50
Hydroxypropyl Cellulose (EF)	0.875
Sodium Lauryl Sulfate	0.35
Outside Powders	
Microcrystalline Cellulose (Granular-102)	18.75
Croscarmellose Sodium	3.5
Magnesium Stearate (vegetable)	0.63
Total	125 mg

EXAMPLE 4

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.0
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Stearic Acid (powder)	3.75
Total	252.5 mg

EXAMPLE 5

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Mannitol	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 6

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Povidone	4.00
Croscarmellose Sodium	9.00
Povidone	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 7

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Povidone	4.00
Croscarmellose Sodium	9.00
Povidone	1.75
Polysorbate 80	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 8

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	157.80
Lactose Monohydrate (spray dried)	25.00
Croscarmellose Sodium	9.00
Hydroxypropyl Methylcellulose	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 9

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	**Quantity (mg)**
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Sucrose	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 10

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EP)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Sodium Stearyl Fumarate	1.25
Total	250 mg

EXAMPLE 11

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
Total	212.50 mg

EXAMPLE 12

By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	Quantity (mg)
Granulation	
Compound A	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Crospovidone	27.00
Hydroxypropyl Cellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
Outside Powders	
Microcrystalline Cellulose (Granular-102)	19.50
Crospovidone	7.00
Magnesium Stearate (vegetable)	1.25
Total	250 mg

EXAMPLE 13

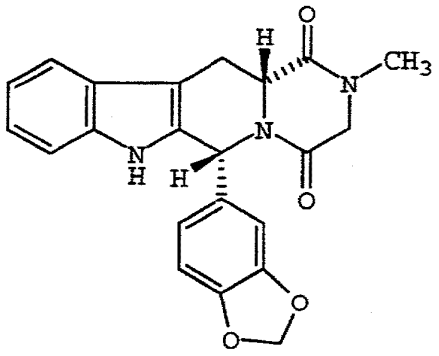
By analogous procedures the following formula was used to prepare a finished dosage form of a tablet providing 10 mg of Compound A, without a film coating.

Ingredient	mg/tablet
Granulation	
Compound A	10.00
Lactose Monohydrate	154.50
Lactose Monohydrate (spray dried)	25.00
Hydroxypropyl Cellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropyl Cellulose (EF)	1.75
Outside Powders	
Microcrystalline Cellulose (Granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate	1.75
Total	**250.0 mg**

The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing specification. The invention that is intended to be protected herein, however, is not construed to be limited to the particular forms disclosed, because they are illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug; a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

2. The formulation of claim 1 further comprising microcrystalline cellulose.

3. The formulation of claim 1 further comprising a wetting agent.

4. The formulation of claim 1 wherein the active compound is present in an amount of about 0.5% to about 10% by weight.

5. The formulation of claim 1 wherein the water-soluble diluent is present in an amount of about 50% to about 85% by weight.

6. The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of a sugar, a polysaccharide, a polyol, a cyclodextrin, and mixtures thereof.

7. The formulation of claim 3 wherein the water-soluble diluent is selected from the group consisting of lactose, sucrose, dextrose, a dextrate, a maltodextrin, mannitol, xylitol, sorbitol, a cyclodextrin, and mixtures thereof.

8. The formulation of claim 1 wherein the lubricant is present in an amount of about 0.25% to about 2% by weight.

9. The formulation of claim 1 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, hydrogenated vegetable oils, and mixtures thereof.

10. The formulation of claim 1 wherein the hydrophilic binder is present in an amount of about 1% to about 5% by weight.

11. The formulation of claim 1 wherein the cellulose derivative is selected from the group consisting of hydroxypropylcellulose, hydroxypropyl methylcellulose, and mixtures thereof.

12. The formulation of claim 1 wherein the disintegrant is present in an amount of about 3% to about 10% by weight.

13. The formulation of claim 2 wherein the microcrystalline cellulose is present in an amount of about 5% to about 40% by weight.

14. The formulation of claim 3 wherein the wetting agent is present in an amount of 0.1% to about 5% by weight.

15. The formulation of claim 14 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, docusate sodium, ethoxylated castor oil, a polyglycolyzed glyceride, an acetylated monoglyceride, a sorbitan fatty acid ester, a poloxamer, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene, a monoglyceride and ethoxylated derivatives thereof, a diglyceride and ethoxylated derivatives thereof, and mixtures thereof.

16. The formulation of claim 1 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, polysorbate 80, and a mixture thereof.

17. The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 40 microns.

18. The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 10 microns.

19. The formulation of claim 1 comprising:

(a) about 1% to about 4% by weight of the active compound;

(b) about 50% to about 75% by weight lactose;

(c) about 0.25% to about 2% by weight magnesium stearate;

(d) about 1% to about 5% by weight hydroxypropyl cellulose; and

(e) about 3% to about 10% by weight croscarmellose sodium.

20. The formulation of claim 18 further comprising about 5% to about 40% by weight microcrystalline cellulose.

21. The formulation of claim 18 further comprising about 0.1% to about 5% by weight sodium lauryl sulfate.

22. A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 20 mg per tablet.

23. A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 to about 15 mg per tablet.

24. A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 mg or about 10 mg per tablet.

25. A capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles, wherein the active compound is present in an amount of about 1 to about 20 mg per capsule.

26. A method of treating sexual dysfunction in a patient in need thereof comprising administering to the patient an effective amount of a formulation of any one of claims 1 through 21.

27. The invention as hereinabove described.

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(54) Title: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Formulations containing a PDE5 inhibitor, a water-soluble diluent, a lubricant, a hydrophilic binder, a disintegrant, and optional microcrystalline cellulose and/or a wetting agent, and their use in treating sexual dysfunction.

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "β-CARBOLINE PHARMACEUTICAL COMPOSITIONS," the specification of which (check one): ☐ is attached hereto; ☐ was filed on _____ as Application Serial No. _____ and was amended on _____ _____ (if applicable); ☒ was filed as PCT International Application No. PCT/US00/11130 on April 26, 2000, and was amended under Article 19 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(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

			Priority Claimed	
PCT/US00/11130	PCT	26/04/00	☒ Yes	☐ No
(Application Serial Number)	(Country)	(Day/Month/Year Filed)		
			☐ Yes	☐ No
(Application Serial Number)	(Country)	(Day/Month/Year Filed)		

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

60/146,924	03/08/99
(Application Serial Number)	(Day/Month/Year Filed)
(Application Serial Number)	(Day/Month/Year Filed)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)
(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)

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 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

37 CFR 1.56. DUTY OF DISCLOSURE - INFORMATION MATERIAL TO PATENTABILITY (Applicable Portion)

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and
(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentability defines, to make sure that any material information contained therein is disclosed to the Office.

Information relating to the following factual situations enumerated in 35 USC 102 and 103 may be considered material under 37 CFR 1.56(a).

35 U.S.C. 102. CONDITIONS FOR PATENTABILITY: NOVELTY AND LOSS OF RIGHT TO PATENT

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. 103. CONDITIONS FOR PATENTABILITY; NON-OBVIOUS SUBJECT MATTER (Applicable Portion)

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.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. 112. SPECIFICATION (Applicable Portion)

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

POWER OF ATTORNEY: I hereby appoint as my attorneys, with full power of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

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#6
#4

Docket No.: 29342/36230A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Oren et al.

Application No.: 10/031,464 Group Art Unit: N/A

Filed: January 17, 2002 Examiner: Not Yet Assigned

For: β-CARBOLINE PHARMACEUTICAL COMPOSITIONS

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

Box Missing Parts
Commissioner for Patents
Washington, DC 20231

Dear Sir:

In response to the Notification of Missing Requirements mailed April 8, 2002, Applicants respectfully submit a Combined Declaration and Power of Attorney.

Our check in the amount of $130.00 covering the fee set forth in 37 CFR 1.16(e) is enclosed. The Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper

05/02/2002 UEDUVIJE 00000098 10031464
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hereafter filed in this application by this firm) to our Deposit Account No. 13-2855, under Order No. 29342/36230A. A duplicate copy of this paper is enclosed.

Dated: April 19, 2002

Respectfully submitted,

By _____

James J. Napoli
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UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/031,464	Peter L. Oren	29342/36230A

INTERNATIONAL APPLICATION NO.	
PCT/US00/11130	
I.A. FILING DATE	PRIORITY DATE
04/26/2000	08/03/1999

04743
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CHICAGO, IL 60606-6357

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MARSHALL GERSTEIN

CONFIRMATION NO. 6930

371 FORMALITIES LETTER

OC000000007803217

Date Mailed: 04/08/2002

Docketed: 6/8/02

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as an Elected Office (37 CFR 1.495):

- U.S. Basic National Fees
- Priority Document
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Preliminary Amendments

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date.

- **$130** Surcharge for providing the oath or declaration later than the appropriate 30 months months from the priority date (37 CFR 1.492(e)) is required.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTH FROM THE DATE OF THIS NOTICE OR BY 22 or 32 MONTHS (where 37 CFR 1.495 applies) FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

Docketed: 6/8/02

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

SUMMARY OF FEES DUE:

Total additional fees required for this application is **$130** for a Large Entity:

- **$130** Late oath or declaration Surcharge.

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)

*A copy of this notice **MUST** be returned with the response.*

BARBARA A CAMPBELL

Telephone: (703) 305-3631

PART 1 - ATTORNEY/APPLICANT COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/031,464	PCT/US00/11130	29342/36230A

FORM PCT/DO/EO/905 (371 Formalities Notice)

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10/031 464

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/031,464	Peter L. Oren	29342/36230A

INTERNATIONAL APPLICATION NO.	
PCT/US00/11130	
I.A. FILING DATE	PRIORITY DATE
04/26/2000	08/03/1999

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CONFIRMATION NO. 6930

371 ACCEPTANCE LETTER

OC000000008138244

Date Mailed: 05/17/2002

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.494 OR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as an 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:

04/29/2002	04/29/2002
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. 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 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:

- U.S. Basic National Fee
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Oath or Declaration
- Preliminary Amendments

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)

BARBARA A CAMPBELL
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PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

PATENT--NO FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1614

Examiner: Unassigned

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents Washington, D.C. 20231.

Dated: **June 20, 2002**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to their duty of disclosure under 37 C.F.R. §1.56, applicants hereby bring to the examiner's attention patents that may be material to the examination of the above-identified application. Therefore, in compliance with 37 C.F.R. §1.97 and §1.98, applicants enclose a completed Form PTO-1449 listing the possibly pertinent patents and a copy of each patent.

This Information Disclosure Statement is submitted more than three months after the filing date of the above-identified application, and, to applicants' knowledge, before the mailing date of a first Office Action on the merits. Therefore, under 37 C.F.R.

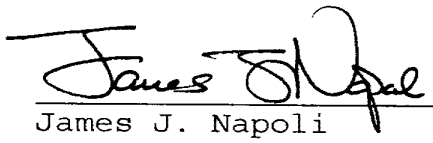
§1.97(b), this Information Disclosure Statement shall be considered by the Patent Office.

The Commissioner, however, is hereby authorized to charge any fee which may be required during the pendency of this application under 37 C.F.R. 1.16 or 37 C.F.R. 1.17 to Deposit Account No. 13-2855. A duplicate copy of this Transmittal is enclosed herewith.

A copy of the International Search Report is enclosed for the convenience of the examiner and to complete the file.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

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Chicago, Illinois
June 20, 2002

Form 1449PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/031,464
Filing Date	April 29, 2002
First Named Inventor	Peter L. Oren et al.
Group Art Unit	1614
Examiner Name	Unassigned
Attorney Docket Number	29342/36230A

U.S. PATENT DOCUMENTS			
Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY

FOREIGN PATENT DOCUMENTS			
Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY
		WO 96/38131 (PCT)	12/05/96
		WO 98/23270 (PCT)	06/04/98
		WO 97/03675 (PCT)	02/06/97

OTHER PRIOR ART – NONPATENT LITERATURE DOCUMENTS		
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*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.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD OF PRODUCING A SOLID DISPERSION OF A POORLY WATER SOLUBLE DRUG

(57) Abstract

Solid dispersions of poorly soluble drugs, to processes for their preparation and their use in pharmaceutical compositions. Specifically, solid dispersions of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione and (+)-N-[1-(adamantanmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1,5benzodiazepin-3-yl]-N'-phenylurea are described.

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METHOD OF PRODUCING A SOLID DISPERSION OF A POORLY WATER SOLUBLE DRUG

The present invention relates to the field of solid dispersions of poorly water soluble drugs, to processes for their preparation and their use in pharmaceutical compositions. More particularly the present invention relates to solid dispersions in the form of co-precipitates of poorly water soluble drugs and their compositions with a pharmaceutically acceptable carrier or excipient therefor. Specifically, the invention relates to co-precipitates of (a) a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) and (b) a potent and selective gastrin and CCK B antagonist, processes for the preparation of such solid dispersions, pharmaceutical compositions containing the same and their use thereof in therapy.

Co-precipitation is a recognised technique for increasing the dissolution of poorly water soluble drugs, such as griseofulvin, ketoprofen, sulphathiazide, spirinolactone, tolbutamide and nifedipine, so as to consequently improve bioavailability thereof. Techniques such as solvent deposition, lyophilization, solvate formation and solid dispersion (of which co-precipitation is an example as described above) have therefore been developed to try to overcome the problem of poor water solubility and resultant low bioavailability.

Solid dispersions in the pharmaceutical field are dispersions of one or more active ingredients, generally poorly water soluble drugs, in an inert carrier or matrix at solid state, which are prepared by either melting the two (fusion), or dissolving them in a solvent, or a combination of approaches, followed by removal of the solvent.

Manufacture of pharmaceutical dispersions by the above referred to melting or fusion technique, involves fusion of the two components where the drug and the carrier are allowed to melt at temperatures at or above the melting point of both the drug and carrier. In the fusion process, the drug and carrier are first blended and both melted in a suitable mixer. The molten mixture is then cooled rapidly to provide a congealed mass which is subsequently milled to produce a powder. The fusion process is technically simple provided that the drug and

carrier are miscible in the molten state but this is not always the case and furthermore, the process is limited in that it tends to lead to drug decomposition due to the high temperatures required to melt the two components.

The solvent-based process uses organic solvents to dissolve and intimately disperse the drug and carrier molecules. Identification of a common solvent for both drug and carrier can be problematic, and complete solvent removal from the product can be a lengthy process. In addition, large volumes of solvents are generally required which can give rise to toxicological problems. The drug and carrier are typically dissolved in a solvent such as methylene chloride, acetone, ethanol and mixtures thereof and the solvent is later removed by precipitation techniques, evaporation or the like, while the drug/carrier solid dispersion is collected as a powdered mass.

In the case where there is difficulty with thermal instability and immiscibility between the drug and the carrier, the hybrid fusion-solvent method can be employed. The drug is first dissolved in a small quantity of organic solvent and added to the molten carrier. The solvent is then evaporated to generate a product that is subsequently milled to produce a powder. The pharmacokinetics, dissolution rates and processes for formulation of many different solid pharmaceutical dispersions is discussed at length in an article by Ford J., in Pharm. Acta. Helv. 61, 3; 69 - 88 (1986).

Co-precipitation techniques employ the use of an organic solvent or solvents to dissolve and intimately disperse the drug and carrier molecules as hereinbefore described. Separation of the drug and carrier from the solvent on precipitation can rely on the solubility properties of either the drug or carrier. For example, Simonelli et al, Journal of Pharmaceutical Sciences, Vol. 58, No. 5, May 1969, describes a co-precipitation process wherein sulfathiazole is dissolved in sodium hydroxide, followed by addition of polyvinylpyrrolidone; hydrochloric acid is then added to effect co-precipitation. This process is based on co-precipitation employing the solubility of the drug at different pH values. Such reliance on the solubility of the drug may be problematic in that it is not generally applicable to poorly water soluble drugs, as many such drugs do not exhibit a pH dependent solubility. Florence et al, Communications, J. Pharm.

Pharmac., 1976, 28 601, describes co-precipitation of trifluoperazine embonate and the polymers poly DL-aspartic acid and polymethylmethacrylate. The co-precipitates were prepared by dissolving the drug and polymer in dimethylformamide and adding the solution to a rapidly stirred volume of water. Both polymers and drug are insoluble in water.

In general terms, problems which can be associated with known co-precipitation techniques can include excess solvent usage, identifying carrier/drug combinations which can be effectively precipitated and enhance bioavailability, the use of heat to effect solution which may detrimentally affect the drug, and the like. Co-precipitation techniques are however attractive for the preparation of solid dispersions, in that less solvents and heat are employed when compared to techniques such as co-evaporation and solvent removal may therefore be facilitated.

We have now developed a co-precipitation technique which alleviates the above described disadvantages associated with known techniques, and have also found that co-precipitation offers an advantageous preparation route for solid dispersions of poorly water soluble drugs.

There is therefore provided in a first aspect of the present invention a process of preparing a solid dispersion comprising a poorly water soluble drug or salts or solvates (e.g. hydrates) thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises:

(i) providing an intimate mixture comprising the carrier or excipient and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water;

(ii) co-mixing the intimate mixture obtained in step (a) with a poorly water soluble drug; and

(iii) co-precipitating the poorly water soluble drug and the carrier or excipient.

As used herein, the term "intimate mixture" can denote a solution, suspension, emulsion, colloid, dispersion or the like. Generally, the term "intimate mixture" as used herein denotes a solution.

It has been found surprisingly that small amounts of water in the intimate mixture can aid dissolution of the subsequently added poorly water soluble drug. For example, a 10% ratio of water in a solvent may aid dissolution of the poorly water soluble drug.

In a further aspect, the invention describes a process of preparing a solid dispersion comprising a particular cGMP specific PDE (PDEV) inhibitor. More particularly, co-precipitation overcomes problems associated with other preparatory processes for formulating the subject PDEV inhibitor.

There is therefore provided by the present invention a process of preparing a solid dispersion comprising (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4- dione (hereinafter referred to as Compound A) or salts or solvates (e.g. hydrates) thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises co-precipitating Compound A and the pharmaceutically acceptable carrier or excipient.

In a yet further aspect, the invention describes a process of preparing a solid dispersion comprising a particular gastrin and CCK-B antagonist. More particularly, co-precipitation overcomes problems associated with other preparatory processes for formulating the subject gastrin and CCK-B antagonist.

There is therefore provided by the present invention a process of preparing a solid dispersion comprising (+)-N-[1-(Adamantanmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro - 1H-1,5benzodiazepin-3-yl]-N'-phenylurea -(hereinafter referred to as Compound B) or salts or solvates (e.g. hydrates) thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises co-precipitating Compound B and the pharmaceutically acceptable carrier or excipient. The synthesis and use of Compound B has been previously described in WO93.14074.

Suitably the co-precipitation of Compound A or B comprises the steps of:

(a) providing an intimate mixture of a poorly water soluble drug selected from Compound A or Compound B, the carrier or excipient therefor and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water; and

(b) co-precipitating the compound and the carrier or excipient.

It is generally advantageous in step (a) to first co-mix the carrier or excipient together with the solvent or solvents and optional water, thereby providing an initial intimate mixture, prior to addition of the poorly water soluble drug thereto. Subsequently, the drug can be added to the initial intimate mixture. Optionally, the carrier or excipient and solvent initial intimate mixture can be subjected to heating sufficient to facilitate dissolving of the former in the latter. Such a sequence of steps (also substantially as hereinbefore described according to the first aspect of the present invention) can be beneficial in allowing the employ of heat to effect dissolving, whilst obviating any detrimental affect by the heat on the drug.

A co-precipitation step, substantially as described in step (iii), or substantially as described in step (b), can aptly comprise adding the drug, carrier or excipient and solvent to a co-precipitation medium in which the carrier or excipient is insoluble. The resultant co-precipitate can be separated from the remaining components, suitably by filtering or the like, and the co-precipitate washed to remove residual solvent, and dried. The co-precipitate can then be formulated in a suitable pharmaceutical form employing known formulatory techniques, substantially as hereinafter described.

The carrier or excipient for the drug, and the co-precipitation medium, are respectively chosen so that the carrier or excipient is substantially insoluble in the co-precipitation medium. It is also advantageous that the carrier or excipient has selected dissolution properties in vivo; for example, the carrier or excipient may be such so as to dissolve rapidly (within about 15 to 60 minutes) in vivo,

alternatively the carrier or excipient may be such so as to dissolve over a relatively prolonged period of time (typically, 2 to 4 hours) so as to achieve sustained release of drug in vivo.

Suitable carrier or excipients include pharmaceutically acceptable polymeric materials, typical examples being hydroxypropyl methyl cellulose phthalate, polymethylacrylate, hydroxypropyl cellulose and other like carrier or excipient materials. Particularly preferred is hydroxypropyl methyl cellulose phthalate as a carrier or excipient, and there is further provided by the present invention co-precipitates consisting of Compound A and hydroxypropyl methyl cellulose phthalate, and Compound B and hydroxypropyl methyl cellulose phthalate.

Aptly the co-precipitation medium comprises an aqueous medium, which is optimally such that the carrier or excipient is substantially insoluble therein as substantially hereinbefore described.

Conveniently the following combinations of carrier or excipient and co-precipitation medium can be employed in a process according to the present invention:

(a) in the case where the carrier or excipient is hydroxypropyl methyl cellulose phthalate, the co-precipitation medium is suitably a weakly acidic medium (pH in the range of 0.5 to 5.0, typically 0.8 to 2.0), typically 0.5N hydrochloric acid or acetic acid;

(b) in the case where the carrier or excipient is an acid soluble polymethylacrylate, the co-precipitation medium is suitably a neutral or basic medium, (pH in the range 6.0 to 13.0), water or dilute alkali being appropriate representatives of suitable co-precipitation media; and

(c) in the case where the carrier or excipient is hydroxypropylcellulose, an appropriate co-precipitation medium is again water, aptly with a temperature of greater than about 40°C, such as 70 to 80°C.

It is of course envisaged that other suitable combinations of carrier or excipient and co-precipitation media may be employed, as will be envisaged by a person skilled in the art. A particularly appropriate combination of carrier or excipient and co-precipitation medium, is hydroxypropyl methyl cellulose phthalate and a dilute acidic medium, substantially as hereinbefore described in point (a) above.

Appropriately, the solvent employed in a process according to the present invention is selected from the group consisting of acetone, methanol, dimethylacetamide, dimethylsulphoxide, dimethylformamide, tetrahydrofuran, and combinations thereof, and optionaly, water, although other suitable solvents could be employed. Generally 9:1 acetone/water, 9:1 tetrahydrofuran/water, or 1:1 acetone/methanol mixtures are employed in a process according to the present invention.

There is still further provided by the present invention a solid dispersion consisting essentially of Compound A or Compound B and a pharmaceutically acceptable carrier or excipient therefor. As a further aspect of the present invention, there is provided hereby a solid dispersion comprising Compound A or Compound B obtainable by a process substantially as hereinbefore described.

It has been shown that Compound A is a potent and selective inhibitor of PDEV. Thus, Compound A is of interest for use in therapy, specifically for the treatment of a variety of conditions where inhibition of PDEV is thought to be beneficial.

As a consequence of the selective PDEV inhibition exhibited, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic, vasodilatory, natriuretic and diuretic activities as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF), nitrovasodilators, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and endothelium-dependent relaxing agents such as bradykinin, acetylcholine and 5-HT_1. Elevated cGMP levels may also mediate relaxation of the corpus cavernosum tissue and consequent penile erection in the teatment of male sexual dysfunction. The solid dispersions of

Compound A therefore have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, diseases characterised by disorders of gut motility (e.g. irritable bowel syndrome), and symptoms associated with male sexual dysfunction.

It will be appreciated that references herein to treatment extend to prophylaxis as well as treatment of established conditions.

There is thus provided as a further aspect of the invention a solid dispersion of Compound A substantially as hereinbefore described for use in therapy, in particular for use in the treatment of conditions where inhibition of PDEV is of therapeutic benefit.

According to another aspect of the invention, there is provided the use of a solid dispersion of Compound A substantially as hereinbefore described for the manufacture of a medicament for use in therapy, in particular the treatment of conditions where inhibition of PDEV is of therapeutic benefit.

In a further aspect, the invention provides a method of treating conditions where inhibition of PDEV is of therapeutic benefit in a human or non-human animal body which comprises administering to said body a therapeutically effective amount of a solid dispersion of Compound A substantially as hereinbefore described.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of Compound A will generally be in the range of from 0.5-800mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day.

Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 0.1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

It has been shown that Compound B is a potent and specific antagonist of gastrin and/or CCK-B. The compound has been shown to be an antagonist of CCK, particularly at CCK-B receptors as demonstrated for example by the compound's ability to inhibit the contractile actions of CCK-4 in the presence of a CCK-A antagonist, in the guinea-pig isolated ileum longitudinal muscle-myenteric plexus.

A solid dispersion of Compound B is therefore useful for the treatment and/or prevention of disorders in mammals, especially humans, where modification of the effects of gastrin or CCK-B is of therapeutic benefit. Thus the solid dispersion of Compound B is useful for the treatment of central nervous system disorders where CCK-B and/or gastrin are involved, for example anxiety disorders (including panic disorder, agoraphobia, social phobia, simple phobia, obsessive compulsive disorders, post traumatic stress disorder, and general anxiety disorder), tardive dyskinesia, depression, Parkinson's disease or psychosis. The solid dispersion of Compound B is also useful for the treatment of gastrointestinal disorders especially those where there is an advantage in lowering gastric acidity. Such disorders include peptic ulceration, reflux oesophagitis and Zollinger Ellison syndrome. It may also be useful for the treatment of gastrointestinal disorders such as irritable bowel syndrome, excess pancreatic secretion, acute pancreatitis, motility disorders, antral G cell hyperplasia, fundic mucosal hyperplasia or gastrointestinal neoplasms. It may also be useful for the treatment of dependency on drugs or substances of abuse and withdrawal, Gilles de la Tourette syndrome, or dysfunction of appetite regulatory systems; as well as the treatment of certain tumours of the lower oesophagus, stomach, intestines and colon. Compounds of the invention are

also useful for directly inducing analgesia, or enhancing opiate or non-opiate mediated analgesia, as well as anaesthesia or loss of the sensation of pain.

There is thus provided as a further aspect of the invention a solid dispersion of compound B substantially as hereinbefore defined for use in the treatment of conditions where modification of the effects of gastrin and/or CCK-B is of therapeutic benefit.

According to another aspect the invention provides the use of a solid dispersion of compound B substantially as hereinbefore defined for the manufacture of a medicament for use in therapy, in particular for the treatment of conditions where modification of the effects of gastrin and/or CCK-B is of therapeutic benefit.

According to a further aspect of the invention we provide a method for the treatment of a mammal, including man, in particular in the treatment of conditions where modification of the effects of gastrin and/or CCK-B is of therapeutic benefit which method comprises administering an effective amount of a solid dispersion of Compound B substantially as hereinbefore defined to the patient.

It will be appreciated that the amount of Compound B required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however doses employed for adult human treatment will typically be in the range of 0.01-2000mg per day e.g 0.01-500mg per day.

For human use, a solid dispersion substantially as hereinbefore described will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally in the form of tablets containing excipients such as cellulose or lactose, or in capsules or ovules either alone or in admixture with excipients.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a solid dispersion substantially as hereinbefore described together with a pharmaceutically acceptable carrier therefor.

There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a solid dispersion substantially as hereinbefore described, which process comprises mixing a solid dispersion substantially as hereinbefore described together with a pharmaceutically acceptable carrier therefor.

A solid dispersion substantially as hereinbefore described may also be used in combination with other therapeutic agents which may be useful in the treatment of the above-mentioned disease states. The invention thus provides, in another aspect, a combination of a solid dispersion substantially as hereinbefore described together with another therapeutically active agent, for simultaneous, separate, or sequential use

The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administered either sequentially or simultaneously in separate pharmaceutical formulations.

Appropriate doses of known therapeutic agents for use in combination with a solid dispersion of the invention will be readily appreciated by those skilled in the art.

Compound B may be prepared by any suitable method known in the art, for example as described in WO93.14074.

Compound A may be prepared by any suitable method known in the art, or as substantially hereinafter described in the accompanying Examples.

The synthesis of Compound A and of intermediates useful in the preparation thereof, are illustrated by the following, non-limiting Examples.

Intermediate 1

(R)-N^a-(3,4-Methylenedioxyphenylcarbonyl)-tryptophan methyl ester

To a suspension of D-tryptophan methyl ester hydrochloride (10.2g) in anhydrous CH_2Cl_2 (150ml) cooled at 0°C was added dropwise triethylamine (12.3ml). To the resulting solution solid piperonyloyl chloride (8.16g) was added portionwise at the same temperature, and the mixture was stirred at room temperature for 2 hours. The mixture was washed successively with water, 0.5N hydrochloric acid, water, a saturated aqueous solution of $NaHCO_3$ and again with water. After drying over Na_2SO_4 and evaporation of the solvent under reduced presure, the resulting oil on trituration from hot cyclohexane afforded the title compound as a white solid (14.7g).

mp : 123-124°C

$[a]_D^{20°}$ = - 84.4° (c = 1.04, $CHCl_3$).

Intermediate 2

(R)-N^a-(3,4-Methylenedioxyphenylthiocarbonyl)-tryptophan methyl ester

A mixture of Intermediate 1 (14g) and Lawesson's reagent (9.28g) in dimethoxyethane (280ml) was heated at 60°C under N_2 for 16 hours with stirring. The reaction mixture was evaporated to dryness and the resulting oil was dissolved in ethyl acetate, then washed successively with an aqueous saturated solution of $NaHCO_3$ and water and dried over Na_2SO_4. The oily residue obtained after evaporation under reduced pressure gave, on trituration from cyclohexane, a yellow powder which was filtered and washed with cooled methanol to afford the title compound (9.74g).

mp : 129-130°C

$[a]_D^{20°}$ = - 186.8° (c = 1.14, $CHCl_3$).

Intermediate 3

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

A solution of Intermediate 2 (9g) and methyl iodide (10ml) in anhydrous dichloromethane (200ml) was heated at reflux under an argon atmosphere with protection from light. After 24 hours, the solvent was removed under reduced pressure to give an orange oil which on trituration from hexane gave a solid which was washed with ether and used without further purification in the next step. This compound (13.11g) was dissolved in methanol (250ml) and the solution was cooled to -78°C. $NaBH_4$ (0.99g) was then added by portions and the mixture was stirred at the same temperature for 1 hour. The reaction was quenched by addition of acetone (10ml) and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water and then with brine and dried over Na_2SO_4. After evaporation of the solvent, the orange oil gave on trituration from a hot mixture of diethyl ether/cyclohexane an orange powder which was recrystallised from diethyl ether/pentane to afford the title compound as a pale yellow solid (5.15g).

mp: 154 - 155°C

$[a]_D^{20}$ = + 24.4° (c = 1.03, CHCl3).

Intermediate 4

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Method A

To a stirred solution of Intermediate 3 (9.7g) and $NaHCO_3$ (2.79g) in anhydrous $CHCl_3$ (200ml) was added dropwise chloroacetyl chloride (5.3ml) at 0°C under N_2. The resulting mixture was stirred for 1 hour at the same temperature and diluted with $CHCl_3$ (100ml). Water (100ml) was then added dropwise with stirring to the mixture, followed by a saturated aqueous solution of $NaHCO_3$. The organic layer was washed with water until neutrality and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the oily compound obtained was crystallised from ether to give the title compound as a pale yellow solid (9.95g).

mp : 233°C

$[a]_D^{20°}$ = - 125.4° (c = 1.17, $CHCl_3$).

Method B

Chloroacetyl chloride (4ml) was added dropwide to a solution of Intermediate 3 (16.1g) and triethylamine (7ml) in anhydrous CH_2Cl_2 (200ml) at 0°C under N_2. The solution was stirred at 0°C for 30 minutes, then diluted with CH_2Cl_2 (300ml). The solution was washed with water (200ml), a saturated aqueous solution of $NaHCO_3$ (300ml) and brine (400ml). After drying over Na_2SO_4 and evaporation under reduced pressure, the resulting solid was washed with ether (300ml) to give the title compound as a pale yellow solid (18.3g).

Example 1

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound A)

To a stirred suspension of Intermediate 4 (12.5g) in MeOH (400ml) was added at room temperature a solution of methylamine (33% in EtOH) (13.7ml) and the resulting mixture was heated at 50°C under N_2 for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (1l). After washing with water (3 x 500ml), drying over Na_2SO_4 and evaporating to dryness, the white solid obtained was recrystallised from 2-propanol to give the title compound as white needles (7.5g).

mp : 298-300°C.

$[a]_D^{20°}$ = + 71.3° (c = 0.55, $CHCl_3$).

Elemental analysis ($C_{22}H_{19}N_3O_4$) calculated: C, 67.86; H, 4.92; N, 10.79;
found: C, 67.79; H, 4.95; N, 10.61%.

Co-precipitation of Compound A :Hydroxypropyl methylcellulose phthalate using acetone/water

	%
Compound A	25 - 90
Hydroxypropyl methylcellulose phthalate (HPMCP)*	10 - 75

* Grades HP55 and HP50.

Compound A (1g) and HPMCP (1g) were dissolved in a 9:1 mixture of acetone/ water (27 ml). 0.25M Hydrochloric acid (83ml) was added. The resultant co-precipitate was filtered,washed with water (5x 3ml), dried in vacuo and milled.

Co-precipitation of Compound A :Hydroxypropyl methylcellulose phthalate using tetrahydrofuran/water

	%
Compound A	25 - 90
Hydroxypropyl methylcellulose phthalate (HPMCP)*	10 - 75

* Grades HP55 and HP50.

Compound A (1g) and HPMCP (1g) were dissolved in a 9:1 mixture of tetrahydrofuran/water (10ml) and the resultant solution was added to a solution of glacial acetic acid (2.25ml) in water (37.7ml). The resultant precipitate was filtered, washed with water (5x3ml), dried in vacuo and milled.

Co-precipitation of Compound B :Hydroxypropyl methylcellulose phthalate using acetone/methanol

	%
Compound B	25 - 90
Hydroxypropyl methylcellulose phthalate (HPMCP)*	10 - 75

* Grades HP55 and HP50.

Compound B (0.65g) and HPMCP (0.65g) were dissolved in a 1:1 mixture of acetone and methanol (35ml). 0.5N Hydrochloric acid (50ml) was added followed by distilled water (50ml). The resultant precipitate was collected, washed with aqueous hydrochloric acid, filtered, and dried in vacuo.

TABLETS FOR ORAL ADMINISTRATION

Co-precipitates of Compound A: HPMCP and Compound B: HPMCP were formulated as follows:

Compound A: HPMCP co-precipitate was blended with the excipients. The resultant mix was compressed into tablets.

1.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	289.2
Colloidal silicon dioxide	0.8
Crospovidone	8.0
Magnesium stearate	2.0

2.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	229.2
Lactose (anhydrous)	52.0
Colloidal silicon dioxide	0.8
Crospovidone	16.0
Magnesium stearate	2.0

3.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	249.2
Polyvinyl pyrrolidone	40.0
Colloidal silicon dioxide	0.8
Crospovidone	8.0
Magnesium stearate	2.0

4.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	281.2
Sodium lauryl sulphate	8.0
Colloidal silicon dioxide	0.8
Crospovidone	8.0
Magnesium stearate	2.0

5.	mg/tablet
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	61.87
Dibasic calcium phosphate anhydrous	62.00
Croscarmellose Sodium	10.00
Sodium lauryl sulphate	5.0
Polyvidone 30	9.38
Colloidal silicon dioxide	0.5
Magnesium stearate	1.25

Compound B: HPMCP co-precipitate was blended with the excipients. The resultant mix was compressed into tablets.

1.	mg/tablet
Compound B: HPMCP co-precipitate	10.0
Microcrystalline cellulose	66.74
Dibasic calcium phosphate anhydrous	66.74
Croscarmellose sodium	6.00
Magnesium stearate	0.53

Tablets of other strengths may be prepared by altering the ratio of Compound A or B: HPMCP co-precipitate to the other excipients.

FILM COATED TABLETS

The aforementioned tablet formulations were film coated.

Coating Suspension	% w/w
Opadry white +	13.2
Purified water	to 100.0*

* The water did not appear in the final product. The maximum theoretical weight of solids applied during coating was 20mg/tablet.

+ Opadry white is a proprietary material obtainable from Colorcon Limited, U.K. which contains hydroxypropyl methylcellulose, titanium dioxide and triacetin.

The tablets were film coated using the coating suspension in conventional film coating equipment.

CAPSULES

1.	mg/capsule
Compound A: HPMCP co-precipitate	100.0
Lactose	168.5
Polyvinyl pyrrolidone	30.0
Magnesium stearate	1.5

The Compound A: HPMCP co-precipitate was blended with the excipients. The mix was filled into size No. O hard gelatin capsules using suitable equipment.

2.	mg/capsule
Compound A: HPMCP co-precipitate	100.0
Microcrystalline cellulose	183.5
Sodium lauryl sulphate	6.0
Crospovidone	9.0
Magnesium stearate	1.5

The Compound A: HPMCP co-precipitate was blended with the excipients. The mix was filled into size No. O hard gelatin capsules using suitable equipment.

3.	mg/capsule
Compound B: HPMCP co-precipitate	10.0
Lactose	90.0
Microcrystalline cellulose	90.0
Crospovidone	7.0
Sodium lauryl sulphate	1.0

Magnesium stearate	2.0

The compound B:HPMCP co-precipitate was blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment. Other strengths may be prepared by altering the ratio of Compound A or B to excipient, the fill weight and if necessary changing the capsule size.

CLAIMS

1. A process of preparing a solid dispersion comprising a poorly water soluble drug or salts or solvates thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises:

(a) providing an intimate mixture comprising the carrier or excipient and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water;

(b) co-mixing the intimate mixture obtained in step (a) with a poorly water soluble drug; and

(c) co-precipitating the poorly water soluble drug and the carrier or excipient.

2. A process as claimed in Claim 1, wherein the carrier or excipient is a polymeric material selected from hydroxypropyl methyl cellulose phthalate, polymethylacrylate, and hydroxypropyl cellulose.

3. A process as claimed in Claim 1 or Claim 2, wherein the co-precipitation medium is selected from a weakly acidic, neutral, or basic medium.

4. A process as claimed in any one of Claims 1-3, wherein the non-aqueous, water miscible solvent employed is selected from acetone, methanol, dimethylacetamide, dimethylsulphoxide, dimethylformamide, tetrahydrofuran, and combinations thereof.

5. A process as claimed in any one of Claims 1-4, wherein the poorly water soluble drug is (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4- dione.

6. A process as claimed in any one of Claims 1-4, wherein the poorly water soluble drug is (+)-N-[1-(adamantanmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro - 1H-1,5benzodiazepin-3-yl]-N'-phenylurea.

7. A process as claimed in Claim 5 wherein the solvent employed is selected from acetone and tetrahydrofuran in a 10% aqueous mixture.

8. A process as claimed in Claim 6 wherein the solvent employed is a combination of acetone and methanol.

9. A process as claimed in any one of Claims 1-8, wherein the carrier or excipient is hydroxypropyl methyl cellulose phthalate.

10. A process as claimed in claim 9, wherein the co-precipitation medium is a weakly acidic medium selected from hydrochloric acid and acetic acid.

11. A process as claimed in any one of Claims 1-8, wherein the carrier or excipient is hydroxypropylcellulose.

12. A process as claimed in Claim 11 wherein the co-precipitation medium is water at an elevated temperature such as 70-80°C.

13. A process as claimed in any one of Claims 1-8, wherein the carrier or excipient is polymethyl acrylate.

14. A process as claimed in Claim 13 wherein the co-precipitation medium is water or dilute alkali.

15. A process of preparing a solid dispersion comprising (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4- dione or salts or solvates thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises:

(a) providing an intimate mixture of a poorly water soluble drug selected from Compound A or Compound B, the carrier or excipient therefor and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water; and

(b) co-precipitating the compound and the carrier or excipient.

16. A process as claimed in Claim 15 wherein the carrier or excipient is hydroxypropyl methyl cellulose phthalate.

17. A process as claimed in Claim 15 or Claim 16, wherein the co-precipitation medium is a weakly acidic medium selected from hydrochloric acid and acetic acid.

18. A process as claimed in any one of Claims 15-17, wherein the solvent employed is selected from acetone and tetrahydrofuran, in a mixture comprising a 10% ratio of water.

19. A process of preparing a solid dispersion comprising (+)-N-[1-(adamantanmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro - 1H-1,5benzodiazepin-3-yl]-N'-phenylurea or salts or solvates thereof, and a pharmaceutically acceptable carrier or excipient therefor, which process comprises:

(a) providing an intimate mixture of a poorly water soluble drug selected from Compound A or Compound B, the carrier or excipient therefor and a non-aqueous, water miscible solvent or combination of solvents, and optionally, water; and

(b) co-precipitating the compound and the carrier or excipient.

20. A process as claimed in Claim 19 wherein the carrier or excipient is hydroxypropyl methyl cellulose phthalate.

21. A process as claimed in Claim 19 or Claim 20, wherein the acidic medium is 0.5N hydrochloric acid.

22. A process as claimed in any one of Claims 19-21, wherein the solvent employed is a combination of acetone and methanol.

23. A solid dispersion consisting of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione and a pharmaceutically acceptable carrier or excipient therefor.

24. A solid dispersion as claimed in Claim 23 for use in therapy.

25. A solid dispersion as claimed in Claim 23 for use in the manufacture of a medicament for the treatment of conditions where inhibition of PDEV is of therapeutic benefit.

26. A method of treating in conditions where inhibition of PDEV is of therapeutic benefit in a human or non-human animal body which comprises administering to said body a therapeutically effective amount of a solid dispersion as claimed in Claim 23.

27. A solid dispersion consisting of (+)-N-[1-(adamantanmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro - 1H-1,5benzodiazepin-3-yl]-N'-phenylurea and a pharmaceutically acceptable carrier or excipient therefor.

28. A solid dispersion as claimed in Claim 27 for use in therapy.

29. The use of a solid dispersion as claimed in Claim 27 for the manufacture of a medicament for the treatment of conditions where modification of the effects of gastrin and/or CCK-B is of therapeutic benefit.

30. A method for the treatment of a mammal, including man, in particular in the treatment of conditions where modification of the effects of gastrin and/or CCK-B is of therapeutic benefit which method comprises administering to the patient an effective amount of a solid dispersion as claimed in Claim 27.

31. A pharmaceutical composition comprising a solid dispersion as claimed in Claim 23 or Claim 24, together with a pharmaceutically acceptable carrier therefor.

32. A process of preparing a pharmaceutical composition comprising a solid dispersion as claimed in Claim 23 or Claim 24, which process comprises mixing said solid dispersion with a pharmaceutically acceptable carrier therefor.

33. A combination of a solid dispersion as claimed in Claim 23 or Claim 24, together with another therapeutically active agent, for simultaneous, separate, or sequential use.

34. A pharmaceutical composition comprising a combination as claimed in Claim 33 together with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 96/02299

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14

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)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 297 866 (THE BOOTS COMPANY PLC) 4 January 1989 see the whole document	1,2,4,11
X,P	WO,A,95 19978 (LABORATOIRES GLAXO) 27 July 1995 see page 32; example 1 see page 71, line 25 - page 74, line 16	23-26, 31,32
X	EP,A,0 558 104 (GLAXO SPA) 1 September 1993 cited in the application see page 40; example 45 see page 41, line 40 - page 43, line 30	27-30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 1996	18. 10. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 96/02299

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-297866	04-01-89	NONE		
WO-A-9519978	27-07-95	AU-A-	1574895	08-08-95
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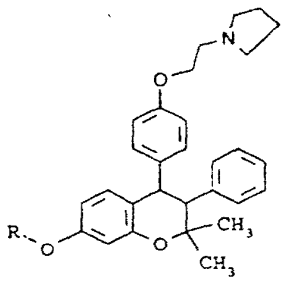

(I)

(57) Abstract

The present invention relates to a pharmaceutical formulation for oral administration which comprises a compound of formula (I) wherein R is C_{1-6} alkyl; or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic binder and a water-soluble diluent.

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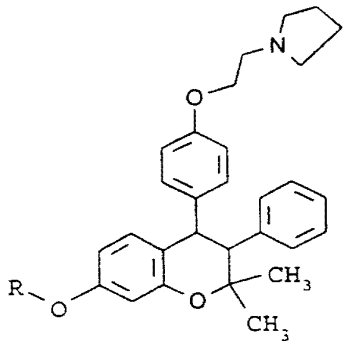
Title

Pharmaceutical formulation.

Field of the Invention

This invention relates to new pharmaceutical formulations for oral administration comprising certain 3,4-diarylchromans of formula I, or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic binder and a water-soluble diluent.

The 3,4-diarylchromans of formula I



(I)

wherein R is C_{1-6}alkyl, and pharmaceutically acceptable salts thereof are known to be useful for reducing bone loss.

Background of the Invention

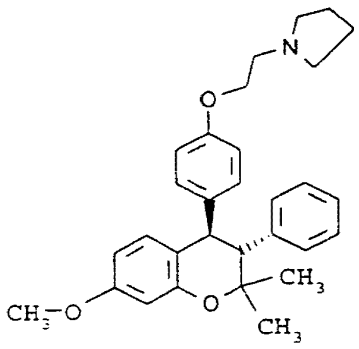
The formula I compounds are described in U.S. Patent No. 5,280,040. This patent describes the preparation of these compounds, as well as their use for reducing bone loss. The preparation of pharmaceutical compositions is also described.

Centchroman, which is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman, is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S. Patent No. 4,447,622; Singh et al., Acta Endocrinal (Copenh) 126 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; Sankaran

et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783. Recently, centchroman as a racemate has been found as a potent cholesterol lowering pharmaceutical agent expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

Levormeloxifene, (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, is a particular preferred compound from this series of 3,4-diarylchromans. Levormeloxifene may be used in human and veterinary medicine for the regulation of bone metabolism. It may be used, for example, in the treatment of patients suffering from bone loss due to osteoporosis (including post-menopausal osteoporosis and glucocorticoid-related osteoporosis), Paget's disease, hyperparathyroidism, hypercalcemia of malignancy and other conditions characterized by excessive rates of bone resorption and/or decreased rates of bone formation.

The 3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent No. 3,340,276 to Carney et al., U.S. Patent No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. The resolvation of (+/-) - 3,4-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane in its optical antipodes is described in U.S. Patent No. 4,447,622 incorporated herein by reference. Example 1 of U.S. Patent No. 4,447,622 describes the preparation of the minus enantiomer, shown by formula II :



(II)

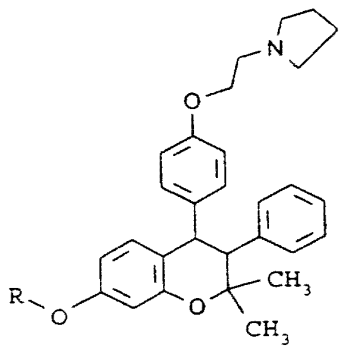
(In this specification, the compound of formula II is referred to as levormeloxifene.) In example 2 of U.S. Patent No. 4,447,622, levormeloxifene is obtained as the free base and the hydrochloride salt.

The compounds of formula I may be administered as pharmaceutically acceptable salts. A particularly useful pharmaceutically acceptable salt of levormeloxifene is the hydrogen fumarate salt (in this specification, this compound is referred to as levormeloxifene fumarate.). This salt form is prepared by dissolving fumaric acid and (-) -3R,4R- trans - 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane in a common solvent such as e.g. methanol, and crystallizing the resulting salt from the solution.

An object of the present invention is to provide a pharmaceutical formulation for oral administration which formulation has a favourable bioavailability.

The present invention provides a pharmaceutical formulation for oral administration comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic carrier composition. Such formulations have an increased solubility in aqueous media.

The present invention provides a pharmaceutical formulation for oral administration which comprises a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof, a hydrophilic binder and a water-soluble diluent. According to a preferred embodiment of the invention, the formulation further comprises a surfactant. The present invention also provides pharmaceutical formulations further comprising a lubricant and/or disintegrant. To further improve the stability of the formulation according to the invention, a suitable antioxidant or a combination of antioxidants may be used. It is preferred to use the compounds of formula I in the trans configuration. The l enantiomeric forms are preferred over racemic mixtures. Within particularly preferred embodiments, R is methyl.

The general chemical terms used in the above formula have their usual meanings.

As used herein, the term "C_{1-6}alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like.

The term "pharmaceutically acceptable salt" represents salt forms of a compound of formula I that are physiologically suitable for pharmaceutical use. The pharmaceutically acceptable salts can exist in conjunction with a compound of formula I as acid addition primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of formula I, wherein R is as defined previously. The alkali metal and alkaline earth metal salts are generally

prepared by the reaction of the metal hydroxide of the desired metal salt with a compound of formula I, wherein R is hydrogen.

Within the present invention, the compounds of formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The term "hydrophilic binder" represents binders commonly used in the formulation of pharmaceuticals, such as polyvinylpyrrolidone, copolyvidone (cross-linked polyvinylpyrrolidone), polyethylene glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, tragacanth, guar, and alginates), gelatin, and cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium carboxymethylcellulose).

The term "water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), and cyclodextrins.

The term "non water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose.

The term "non water-soluble diluent with non-swelling properties" represents the non water-soluble diluents as indicated above, but excluding starches and modified starches and the like.

The term "surfactant", as used herein, represents ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides,

sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids.

The term "antioxidant" represents the three groups of antioxidants, true antioxidants, reducing agents and antoxidant synergists, such as tocopherols, tocopherolesters, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, citric acid, edetic acid and its salts, lecithin and tartaric acid.

The term "disintegrant" represents compounds such as starches, clays, celluloses, alginates, gums, cross-linked polymers (such as cross-linked polyvinylpyrrolidone and cross-linked sodium carboxymethylcellulose), sodium starch glycolate, low-substituted hydroxypropyl cellulose, and soy polysaccharides. Preferably, the disintegrant is a modified cellulose gum such as e.g. cross-linked sodium carboxymethylcellulose.

The term "lubricant" represents compounds frequently used as lubricants or glidants in the preparation of pharmaceuticals, such as talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, magnesium carbonate, magnesium oxide, calcium silicate, microcrystalline cellulose, starches, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, sodium laurylsulfate, sodium stearyl fumarate, and hydrogenated vegetable oils. Preferably, the lubricant is magnesium stearate or talc, more preferably magnesium stearate and talc in combination.

All formulations of the present invention have an increased solubility in aqueous media and therefore, greater bioavailability would be expected. In a bioavailability study in humans comparing a solution of levormeloxifene and a levormeloxifene tablet formulation a bioequivalency of 100% was obtained.

In one preferred embodiment of the invention, the hydrophilic binder is gelatin, cellulose derivative, polyvinylpyrrolidone or copolyvidone.

In another preferred embodiment of the invention, the water-soluble diluent is a sugar, a polysaccharide or cyclodextrin.

In another preferred embodiment of the invention, the formulation further comprises a non water-soluble diluent. In one embodiment thereof the non water-

soluble diluent is a non water-soluble diluent with non-swelling properties, preferably microcrystalline cellulose.

In another preferred embodiment of the invention, the formulation further comprises an antioxidant. Preferably the antioxidant is tocopherols and tocopherolesters, such as alpha-tocopherol succinate.

In another preferred embodiment of the invention, the formulation further comprises a surfactant. When the surfactant is present, preferably it is an anionic or nonionic surfactant. Representative surfactants from this preferred group include sodium laurylsulfate, polyglycolyzed glycerides, polyoxyethylene sorbitan fatty acid esters, monoglycerides, diglycerides or glycerol.

In another preferred embodiment of the invention, the formulation further comprises a lubricant(s) and/or a disintegrant.

Certain formulations of the present invention are more preferred. More preferably, the hydrophilic binder is polyvinylpyrrolidone or copolyvidone. More preferably, the water-soluble diluent is a sugar, such as lactose, sucrose, dextrose. More preferably, the surfactant is a nonionic surfactant, such as polyoxyethylene sorbitan fatty acid esters or glycerol.

Certain formulations of the present invention are most preferred. Most preferably, the hydrophilic binder is copolyvidone. Most preferably, the water-soluble diluent is lactose. Most preferably, the surfactant, when present, is glycerol.

The amount of hydrophilic binder in the pharmaceutical formulation according to the invention is preferably from about 1% to about 25% (w/w), more preferably from about 1% to about 15% (w/w), most preferably from about 2,5% to about 15% (w/w).

The amount of water-soluble diluent in the pharmacutical formulation according to the invention is preferably from about 20% to about 98% (w/w), more preferred from about 20% to about 80% (w/w).

The amount of non water-soluble diluent in the pharmacutical formulation according to the invention is preferably from about 1% to about 50% (w/w), more preferred from about 5% to about 30% (w/w).

The amount of the compound of formula I in the pharmaceutical formulation according to the invention is preferably from about 0,05% to about 50% (w/w), such as from about 0,1% to about 40% (w/w).

The orally administerable formulations of the present invention are prepared and administered according to methods well known in pharmaceutical chemistry, see Remington's Pharmaceutical Sciences, 17th ed. (A. Osol ed., 1985). For example, the compositions of the present invention may be administered by means of solid dosage forms such as tablets and capsules. Preferably, the compositions are formulated as tablets. These tablets may be prepared by wet granulation, by dry granulation, or by direct compression.

Tablets for this invention are prepared utilizing conventional tabletting techniques. A general method of manufacture involves blending of a compound of formula I, or a salt thereof, the water-soluble diluent, hydrophilic binder and optionally a portion of a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant and milled, if necessary. The granules are dried and reduced to a suitable size. Any other ingredients, such as lubricants, (e.g. magnesium stearate) and additional disintegrants, are added to the granules and mixed. This mixture is then compressed into a suitable size and shape using conventional tabletting machines such as a rotary tablet press. The tablets may be film coated by techniques well known in the art.

Capsules for this invention are prepared utilizing conventional methods. A general method of manufacture involves blending of a compound of formula I, or a salt thereof, the water-soluble diluent, a hydrophilic binder, and optionally a portion of a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant in water, and milled, if necessary.

The granules are dried and reduced to a suitable size. Any other ingredients, such as a lubricant, are added to the granules and mixed. The resulting mixture is then filled into a suitable size hard-shell gelatin capsule using conventional capsule-filling machines.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

The preferred range of pharmaceutical formulation (such as solid dosage form, e.g. capsule or tablet) strength may be from about 0.125 mg to about 40 mg of a compound of formula I, more preferred from about 0.25 mg to about 5 mg of a compound of formula I, preferably levormeloxifene.

The preferred range of total mass may be from about 40 mg to about 500 mg depending on the strength of the formulation, more preferred from about 80 mg to about 320 mg.

Tablets and capsules may be prepared using the ingredients and procedures as described below:

Formulation 1

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 10 mg base	12.54 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg
Copolyvidone	24.00 mg
Lactose	206.00 mg
Magnesium stearate	1.00 mg
Talc	3.20 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 320 mg.

Formulation 2

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 5 mg base	6.27 mg
Microcrystalline cellulose	24.00 mg
Cross-carmellose sodium	12.50 mg
Copolyvidone	12.00 mg
Lactose	102.85 mg
Magnesium stearate	0.80 mg
Talc	1.60 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous

solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.25 mg to 40 mg with a total mass of 160 mg.

Formulation 3

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 5 mg base	6.27 mg
Microcrystalline cellulose	18.00 mg
Cross-carmellose sodium	9.36 mg
Copolyvidone	9.00 mg
Lactose	75.57 mg
Magnesium stearate	0.60 mg
Talc	1.20 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.125 mg to 20 mg with a total mass of 120 mg.

Formulation 4

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg
Copolyvidone	24.00 mg
Na-laurylsulfate	6.40 mg
Lactose	161.80 mg
Magnesium stearate	1.60 mg
Talc	3.20 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing dissolved sodium laurylsulfate. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40mg with a total mass of 320 mg.

Formulation 5

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Dextrose	168.20 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg
Copolyvidone	24.00 mg
Magnesium stearate	1.60 mg
Talc	3.20 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 320 mg.

Formulation 6

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	70.00 mg
Cross-carmellose sodium	31.25 mg
Gelatine	5.00 mg
Lactose	237.75 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 7

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	70.00 mg
Cross-carmellose sodium	31.25 mg
Dextrose	237.75 mg
Gelatine	5.00 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 8

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	60.00 mg
Cross-carmellose sodium	31.25 mg
Copolyvidone	25.00 mg
Tween 80	3.25 mg
Lactose	224.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing Tween 80. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 9

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	60.00 mg
Cross-carmellose sodium	31.25 mg
Copolyvidone	29.00 mg
Glycerol	3.25 mg
Lactose	220.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 10

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	68.00 mg
Cross-carmellose sodium	26.25 mg
Gelatine	5.00 mg
Glycerol	6.25 mg
Dextrose	338.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine and glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass of 400 mg.

Formulation 11

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	35.00 mg
Cross-carmellose sodium	26.25 mg
hydroxypropyl-betacyclodextrin (HP-cd)	115.00 mg
Gelatine	5.00 mg
Glycerol	6.25 mg
Dextrose	256.50 mg
Magnseium stearate	2.00 mg
Talc	4.00

The mixture of levormeloxifene fumarate, dextrose, hydroxypropyl-betacyclodextrin microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine containing glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 500 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 80 mg with a total mass of 500 mg.

Formulation 12 and 13

Ingredient	Weight
Levormeloxifene fumarate corresponding to 5 mg base	6.27 mg
Lactose	395.1 mg
Microcrystalline cellulose	9.875 mg
Polyvinylpyrrolidone/copolyvidone	8.400 mg
Magnesium stearate	0.375 mg

The mixture of levormeloxifene fumarate, lactose and microcrystalline cellulose is granulated with an aqueous solution of polyvinylpyrrolidone or copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate. The mixture is then filled into size 0 hard-shell gelatine capsules utilizing conventional encapsulating equipment. In order to obtain different capsule strenghts in the range of 1.25 mg to 20.0 mg, different quantities are weighed out in the range of 15 mg to 240 mg.

Formulation 14

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.313 mg
Microcrystalline Cellulose	12.00 mg
Cross-Carmellose Sodium	6.25 mg
Copolyvidone	6.00 mg
Lactose	54.20 mg
Alpha-tocopherol Succinate	0.0308 mg
Magnesium Stearate	0.40 mg
Talc	0.80 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, antioxidant, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 80 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.125 mg to 10 mg with a total mass of 80 mg.

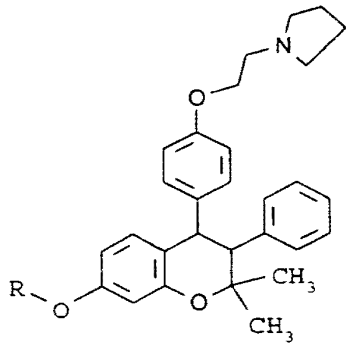
Formulation 15

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	3.13 mg
Microcrystalline Cellulose	15.00 mg
Cross-Carmellose Sodium	7.75 mg
Copolyvidone	7.50 mg
Lactose	64.80 mg
Alpha-tocopherol Succinate	0.0308 mg
Magnesium Stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, antioxidant, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 100 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.125 mg to 20 mg with a total mass of 100 mg.

Claims

1. A pharmaceutical formulation for oral administration which comprises a compound of formula I



(I)

wherein R is C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof, in combination with a hydrophilic binder and a water-soluble diluent.

2. The formulation according to claim 1 wherein said hydrophilic binder is copolyvidone or cross-linked polyvinylpyrrolidone.

3. The formulation according to Claim 1 or 2 wherein said water-soluble diluent is lactose.

4. The formulation according to any one of Claims 1-3 further comprising a surfactant.

5. The formulation according to Claim 4 wherein said surfactant is glycerol.

6. The formulation according to any one of the preceding claims comprising a compound of formula I, lactose, copolyvidone, talc, magnesium stearate, microcrystalline cellulose and cross-carmellose sodium.

7. The formulation according to any one of the preceding claims further comprising an antioxidant.

8. The formulation according to claim 7 wherein said antioxidant is alpha-tocopherol succinate.

9. The formulation according to any one of the preceding claims further comprising a non water-soluble diluent.

10. The formulation according to claim 9 wherein said non water-soluble diluent is microcrystalline cellulose.

11. The formulation according to any one of the preceding claims wherein said formulation is a solid dosage form.

12. The formulation according to claim 11 wherein said dosage form is a tablet.

13. The formulation according to any one of the preceding claims further comprising a film coating.

14. The formulation according to any one of the preceding claims wherein R in the compound of formula I is methyl.

15. The formulation according to any one of the preceding claims wherein said compound of formula I is in the trans configuration.

16. The formulation according to any one of the preceding claims wherein said compound of formula I is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman or a salt thereof.

17. The formulation according to any one of the preceding claims wherein said compound of formula I is an isolated l-enantiomer or a salt thereof.

18. The formulation according to any one of the preceding claims wherein said compound of formula I is (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane or a salt thereof.

19. The formulation according to claim 18 wherein said compound of formula I is in the form of the hydrogen fumarate salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00543

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 9/20
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)

IPC6: A61K

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

SE,DK,FI,NO classes as above

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

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5407955 A (HENRY U. BRYANT ET AL), 18 April 1995 (18.04.95), see column 11 and 12	1-19
X	US 5482958 A (HENRY U. BRYANT ET AL), 9 January 1996 (09.01.96), see column 11 and 12	1-19
X	US 5472977 A (HENRY U. BRYANT ET AL), 5 December 1995 (05.12.95), see column 11 and 12	1-19
X	US 5563133 A (PHILIP A. HIPSKIND), 8 October 1996 (08.10.96), see formulation example 4 and 11	1-19

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
25 February 1998	03 -03- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00543

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4447622 A (MOHAMMAD SALMAN ET AL), 8 May 1984 (08.05.84) --	1-19
A	US 5464862 A (VIRENDER M. LABROO ET AL), 7 November 1995 (07.11.95) --	1-19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.
PCT/DK 97/00543

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		WO 9420098 A	15/09/94

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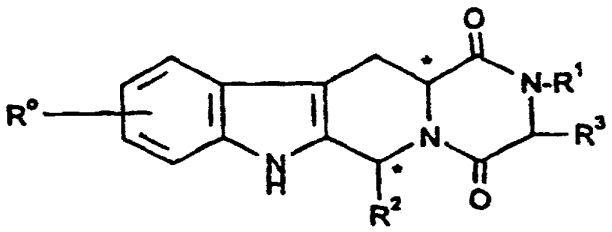
Published
With international search report.

(54) Title: USE OF CGMP-PHOSPHODIESTERASE INHIBITORS TO TREAT IMPOTENCE

(57) Abstract

The use of compounds of formula (I) (6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, (3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, and physiologically acceptable salts and solvates thereof, in the treatment of impotence.



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USE OF CGMP-PHOSPHODIESTERASE INHIBITORS TO TREAT IMPOTENCE

This invention relates to the use of tetracyclic derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) in the treatment of impotence.

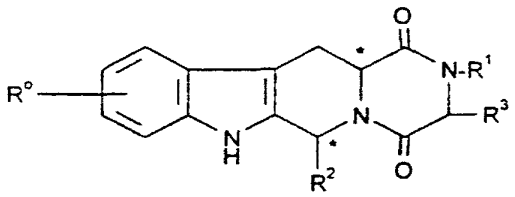
Impotence can be defined as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c. injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). GB 9514464.8, which is the priority document for the present application describes the syntheses of the compounds of the invention and their utility in impotence. WO95/19978, which

was unpublished at the priority date of the present application, also describes the syntheses of the compounds of the invention and their utility in other diseases associated with inhibition of cGMP PDEs. The compounds may be represented by the following general formula (I):

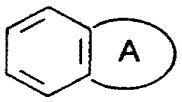


(I)

and salts and solvates (e.g. hydrates) thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Suitable individual compounds of the invention for use in the treatment of erectile dysfunction include:

Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1] pyrido [3,4-b] indole-1,4-dione;
(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;
(3S, 6R,12aR)-2,3,6,7,12,12a-hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The specific compounds of the invention are:

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione (Compound A); and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione (Compound B);

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Unexpectedly, it has now been found that compounds of formula (I), and in particular compounds A and B, are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby

obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of compounds of formula (I), and in particular compounds A and B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

The pharmaceutically acceptable salts of the compounds of formula (I), and in particular compounds A and B which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of formula (I), and in particular compounds A and B can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP specific PDE. It has now been surprisingly found that human corpus cavernosum contains three distinct PDE enzymes. The predominant PDE has further surprisingly been found to be cGMP PDE. As a consequence of the selective PDE V inhibition exhibited by compounds of the present invention, the subject compounds can elevate cGMP levels, which in turn can mediate relaxation of the corpus cavernosum tissue and consequent penile erection.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I), and in particular compounds A and B will generally be in the range of from 0.5-800mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for buccal or sublingual administration will typically be within the range of from 0.1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, compounds of formula (I), and in particular compounds A and B can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agents (e.g. methylcellulose, a semi-synthetic glyceride such as witepsol or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters or mixtures of PEG-8 and caprylic/capric glycerides).

For veterinary use, a compound of formula (I), and in particular compound A or B or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Thus the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

There is further provided a process for the preparation of a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

Moreover, the invention includes the use of a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

A compound of formula (I), and in particular compound A or B, may also be used in combination with other therapeutic agents which may be useful in the treatment of erectile dysfunction substantially as hereinbefore described. The invention thus provides, in another aspect, a combination of a compound of formula (I), and in particular compound A or B together with another therapeutically active agent.

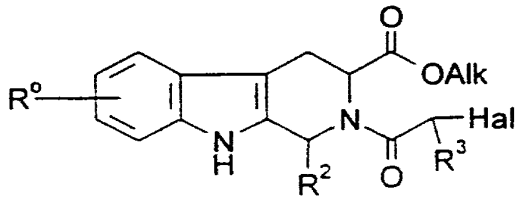
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administered either sequentially or simultaneously in separate pharmaceutical formulations.

Appropriate doses of known therapeutic agents for use in combination with a compound of the invention will be readily appreciated by those skilled in the art.

The compounds of the invention may be prepared by any suitable method known in the art or by the following process which forms part of the present invention. The process has been previously substantially described in the priority document of the present invention GB9514464.8, and in WO95/19978.

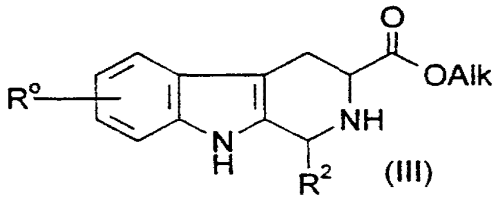
Thus, a process for preparing a compound of formula (I) comprises treating a compound of formula (II)



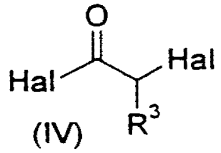
(II)

(in which Alk represents C_{1-6}alkyl, e.g. methyl or ethyl and Hal is a halogen atom, e.g. chlorine) with a primary amine R^1NH_2 in a suitable solvent such as an alcohol (e.g. methanol or ethanol) or a mixture of solvents, conveniently at a temperature of from 20°C to reflux (e.g. at about 50°C).

A compound of formula (II) may conveniently be prepared by treating a compound of formula (III) with a compound of formula (IV)



(III)



(IV)

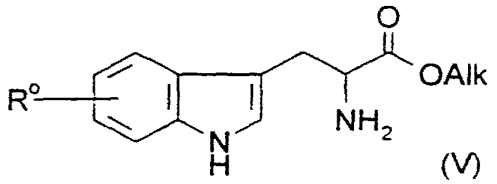
in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g. $NaHCO_3$). The reaction may conveniently be effected at a temperature of from -20°C to +20°C (e.g. at about 0°C).

A compound of formula (I) may also be prepared from a compound of formula (III) in a two-step procedure via a compound of formula (II) isolated without purification.

Compounds of formula (I) may be prepared as individual enantiomers in two steps from the appropriate enantiomer of formula (III) or as mixtures (e.g. racemates) of either pairs of cis or trans isomers from the correspondong mixtures of either pairs of cis or trans isomers of formula (III).

Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using HPLC (high performance liquid chromatography) on a chiral column such as Hypersil naphthylurea.

A compound of formula (III) may conveniently be prepared from a tryptophan alkyl ester of formula (V)



(V)

(where Alk is as previously defined) or a salt thereof (e.g. the hydrochloride salt) with an aldehyde R^2CHO. The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as trifluoroacetic acid. The reaction may conveniently be carried out at a temperature of from -20°C to reflux to provide a compound of formula (III) in one step. The reaction may also be carried out in a solvent such as an aromatic hydrocarbon (e.g. benzene or toluene) under reflux, optionally using a Dean-Stark apparatus to trap the water produced.

The reaction provides a mixture of cis and trans isomers which may be either individual enantiomers or racemates of pairs of cis or trans isomers depending upon whether racemic or enantiomerically pure tryptophan alkyl ester was used as the starting material. Individual cis or trans enantiomers may conveniently be separated from mixtures thereof by fractional crystallisation or by chromatography (e.g. flash column chromatography) using appropriate solvents and eluents. Similarly, pairs of cis and trans isomers may be separated by chromatography (e.g. flash column chromatography) using appropriate eluents. An optically pure trans isomer may also be converted to an optically pure cis isomer using suitable epimerisation procedures. One such procedure comprises treating the trans isomer or a mixture (e.g. 1 : 1 mixture) of cis and trans isomers with methanolic or aqueous hydrogen chloride at a temperature of from 0°C to the refluxing temperature of the solution. The mixture may then be subjected to chromatography (e.g. flash column chromatography) to separate the resulting diastereoisomers, or in the procedure utilising aqueous hydrogen chloride the

desired cis isomer precipitates out as the hydrochloride salt which may then be isolated by filtration.

The pharmaceutically acceptable acid addition salts of a compound of formula (I), and in particular compound A or B which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of compound A or B with a suitable base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

Compounds of the invention may be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent.

The syntheses of compounds A and B and of the intermediates for use therein are illustrated by the following examples. The examples have been previously described in the priority document of the instant invention GB9514464.8, and the corresponding Intermediate or Example numbers therein are shown in parentheses next to the current Intermediate or Example number.

In the Examples section hereinafter the following abbreviations are used:

MeOH (methanol) and EtOH (ethanol),

Intermediate 1 (54)

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

To a stirred solution of D-tryptophan methyl ester (11 g) and piperonal (7.9 g) in anhydrous CH_2Cl_2 (400 mL) cooled at 0°C was added dropwise trifluoroacetic acid (7.7 mL) and the solution was allowed to react at ambient temperature. After 4 days, the yellow solution was diluted with CH_2Cl_2 (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$, then with water (3x200 mL) and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure and the residue containing the two geometric isomers was purified by flash

chromatography eluting with dichloromethane/ethyl acetate (97/3) to give as the firsr eluting product the title compound (6.5 g)

m.p. : 154°C

Intermediate 2 (83)

(1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-(2-chloropropionyl)-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

To a solution of (R)-(+)-2-chloropropionic acid (191 µl, 2.2 mmol) in anhydrous dichloromethane (30 mL), was added dicyclohexylcarbodiimide (0.45 g, 2.2. mol). Intermediate 1 (0,7 g, 2 mmol) was then added and the mixture was stirred at room temperature for 20 hours. The formed precipitate of dicyclohexylurea was removed by filtration, the filtrate was evaporated in vacuo and the crude product was purified by flash chromatography eluting with toluene/ethyl acetate : 95/5. The oily compound obtained was then crystallised from ether/hexane to give the title compound as pale yellow crystals (0.74 g)

m.p. : 126-128°C.

Example 1 (78) (Compound A)

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione

a) To a stirred solution of intermediate 1 (0.5 g) and $NaHCO_3$ (0.14 g) in anhydrous $CHCl_3$ (20 mL) was added dropwise chloroacetyl chloride (0.27 mL) at 0°C. The resulting mixture was stirred for 1 hour at the same temperature and diluted with $CHCl_3$ (20 mL). Water (10 mL) was then added dropwise with stirring to the mixture, followed by a saturated solution of $NaHCO_3$. The organic layer was washed with water until neutrality and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, (6R,12aR)-methyl 1,2,3,4-tetrahydro-2-chloroacetyl-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate was obtained as an oil which was crystallised from ether to give a solid (0.38 g, m.p. : 233°C) which was used without further purification in the next step.

b) To a stirred suspension of the chloroacetyl intermediate (0.37 g) in MeOH (20 mL) was added at room temperature a solution of methylamine (33% in

EtOH) (0.4 mL) and the resulting mixture was heated at 50°C under N_2 for 16 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (3x20 mL), drying over Na_2SO_4 and evaporating to dryness, the residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (99/1) and recrystallised from 2-propanol to give the title compound as white crystals (0.22 g)

m.p. : 302-303°C.

Analysis for $C_{22}H_{19}N_3O_4$:

Calculated:C,67.86;H,4.92;N,10.79;

Found:C,67.77;H,4.92;N,10.74%.

$[\alpha]^{20°}_D$ = +71.0° (C=1.00; $CHCl_3$).

Example 2 (117) (Compound B)

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

To a stirred solution of intermediate 2 (0.3 g, 0.68 mmol) in THF (30 mL) was added at room temperature a solution of methylamine (33 % in EtOH) (0.68 mL) and the resulting solution was treated at reflux under N_2 for 6 days. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (2,25 mL), drying over Na_2SO_4 and evaporating to dryness, the crude product was purified by flash chromatography eluting with dichloromethane/methanol : 99/1. The oily residue obtained was crystallised from methanol to give the title compound as white crystals (40 mg) m.p. : 307-309°C.

Analysis for $C_{23}H_{21}N_3O_4$:

Calculated : C, 68.47 ; H, 5.25 ; N, 10.42 ;

Found : C, 68.35; H, 5.33; N, 10.42%.

$[\alpha]^{20°}_D$ = + 65.2° (c = 1.15 ; $CHCl_3$).

The following compound was similarly prepared:

Example 3

(3S, 6R,12aR)-2,3,6,7,12,12a-Hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione as white crystals using ammonia as the base.

m.p. : 319-321°C.

Analysis for $C_{22}H_{19}N_3O_4$:

Calculated : C, 67.86 ; H, 4.92 ; N, 10.79 ;

Found : C, 67.86; H, 5.17; N, 10.72%.

$[\alpha]^{20°}_D$ = + 107° (c = 1 ; pyridine).

Compounds A and B have been included in pharmacy formulations and details of such formulations are given below.

TABLETS FOR ORAL ADMINISTRATION

A. Direct Compression

1.	mg/tablet
Active ingredient	50.0
Crospovidone USNF	8.0
Magnesium Stearate Ph Eur	1.0
Anhydrous Lactose	141.0

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

2.	mg/tablet
Active ingredient	50.0
Colloidal Silicon Dioxide	0.5
Crospovidone	8.0
Sodium Lauryl Sulphate	1.0
Magnesium Stearate Ph Eur	1.0
Microcrystalline Cellulose USNF	139.5

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

B. WET GRANULATION

1.	mg/tablet
Active ingredient	50.0
Polyvinyl pyrollidone	150.0
Polyethylene glycol	50.0
Polysorbate 80	10.0
Magnesium Stearate Ph Eur	2.5
Croscarmellose Sodium	25.0
Colloidal Silicon Dioxide	2.5
Microcrystalline Cellulose USNF	210.0

The polyvinyl pyrollidone, polyethylene glycol and polysorbate 80 were dissolved in water. The resultant solution was used to granulate the active ingredient. After drying the granules were screened, then extruded at elevated temperatures and pressures. The extrudate was milled and/or screened then was blended with the microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The resultant mix was compressed into tablets.

2.	mg/tablet
Active ingredient	50.0
Polysorbate 80	3.0
Lactose Ph Eur	178.0
Starch BP	45.0
Pregelatinised Maize Starch BP	22.5
Magnesium Stearate BP	1.5

The active ingredient was sieved and blended with the lactose, starch and pregelatinised maize starch. The polysorbate 80 was dissolved in purified water. Suitable volumes of the polysorbate 80 solution were added and the powders were granulated. After drying, the granules were screened and blended with the magnesium stearate. The granules were then compressed into tablets.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to the other excipients.

FILM COATED TABLETS

The aforementioned tablet formulations were film coated.

Coating Suspension	% w/w

Opadry white†	13.2
Purified water Ph Eur	to 100.0*

* The water did not appear in the final product. The maximum theoretical weight of solids applied during coating was 20mg/tablet.

† Opadry white is a proprietary material obtainable from Colorcon Limited, UK which contains hydroxypropyl methylcellulose, titanium dioxide and triacetin.

The tablets were film coated using the coating suspension in conventional film coating equipment.

CAPSULES

1.	mg/capsule
Active ingredient	50.0
Lactose	148.5
Polyvinyl pyrollidone	100.0
Magnesium Stearate	1.5

The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

2.	mg/capsule
Active ingredient	50.0
Microcrystalline Cellulose	233.5
Sodium Lauryl Sulphate	3.0

Crospovidone	12.0
Magnesium Stearate	1.5

The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

Other doses may be prepared by altering the ratio of active ingredient to excipient, the fill weight and if necessary changing the capsule size.

3.	mg/capsule
Active ingredient	50.0
Labrafil M1944CS	to 1.0 ml

The active ingredient was sieved and blended with the Labrafil. The suspension was filled into soft gelatin capsules using appropriate equipment.

Inhibitory effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells at al. (Wells, J. N., Baird, C. E., Wu, Y. J. and Hardman, J. G., Biochim. Biophys. Acta 384, 430 (1975)). The reaction medium contained 50mM Tris-HCl,pH 7.5, 5mM Mg-acetate, 250μg/ml 5'-Nucleotidase, 1mM EGTA and 0.15μM 8-[H^3]-cGMP. The enzyme used was a human recombinant PDE V (ICOS, Seattle USA).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC_{50} values for the compounds examined were determined from concentration-response curves using typically concentrations ranging from 10nM to 10μM. Tests against other PDE enzymes using standard methodology also

showed that compounds of the invention are highly selective for the cGMP specific PDE enzyme.

-cGMP level measurements

Rat aortic smooth muscle cells (RSMC) prepared according to Chamley et al. in Cell Tissue Res. 177, 503 - 522 (1977) were used between the 10th and 25th passage at confluence in 24-well culture dishes. Culture media was aspirated and replaced with PBS (0.5ml) containing the compound tested at the appropriate concentration. After 30 minutes at 37°C, particulates guanylate cyclase was stimulated by addition of ANF (100nM) for 10 minutes. At the end of incubation, the medium was withdrawn and two extractions were performed by addition of 65% ethanol (0.25ml). The two ethanolic extracts were pooled and evaporated until dryness, using a Speed-vac system. c-GMP was measured after acetylation by scintillation proximity immunoassay (AMERSHAM).

The compounds according to the present invention were typically found to exhibit an IC_{50} value of less than 500nM, and an EC_{50} value of less than 5. In vitro test data for representative compounds of the invention is given in following Table 1:

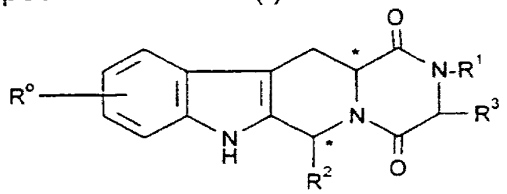
Table 1

Example No.	IC_{50} nM	EC_{50} μM
1	2	0.2
2	2	0.2

The above data demonstrates the ability of the subject compounds of the invention to inhibit cGMP PDE, and hence their utility in the treatment of erectile dysfunction substantially as hereinbefore described.

CLAIMS

1. Use of a compound of formula (I):

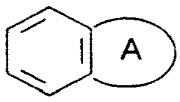


(I)

and salts and solvates (e.g. hydrates) thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain;

for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

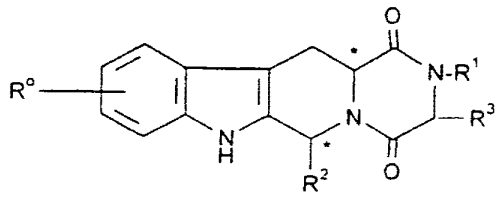
2. Use of a compound selected from

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione; and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione;

and physiologically acceptable salts and solvates thereof for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

3. Method for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising administration of a compound of formula (I):

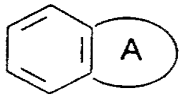


(I)

and salts and solvates (e.g. hydrates) thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

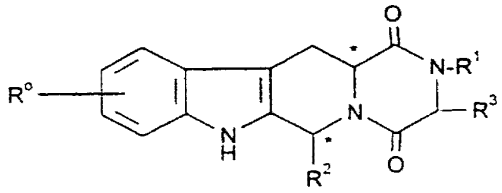
4. Method for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising administration of a compound selected from

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione; and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

and physiologically acceptable salts and solvates thereof.

5. A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I):

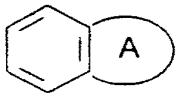


(I)

and salts and solvates (e.g. hydrates) thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring 

attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain;

together with a pharmaceutically acceptable diluent or carrier.

6. A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound selected from

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione; and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

and physiologically acceptable salts and solvates thereof, together with a pharmaceutically acceptable diluent or carrier.

7. A process for the preparation of a pharmaceutical composition according to Claim 5 for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), and physiologically acceptable salts and solvates thereof, with a pharmaceutically acceptable diluent or carrier.

8. A process for the preparation of a pharmaceutical composition according to Claim 6 for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound selected from

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione; and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

and physiologically acceptable salts and solvates thereof, with a pharmaceutically acceptable diluent or carrier.

9. A method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a pharmaceutical composition according to Claim 5 or 6.

10. Use of a pharmaceutical composition according to Claim 5 or 6, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

11. A combination of a compound selected from

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione; and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-1,4-dione

and physiologically acceptable salts and solvates thereof, together with another therapeutically active agent, for simultaneous, separate, or sequential use in the treatment of erectile dysfunction in a male animal, including man.

12. A pharmaceutical formulation comprising a combination according to Claim 11 together with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/03024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495

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)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. UROL., vol. 152, no. 6 pt 1, 1994, pages 2159-2163, XP000604575 C. SPARWASSER ET AL.: "Smooth muscle tone regulation in rabbit cavernosal and spongiosal tissue by cyclic AMP- and cyclic GMP-dependent mechanisms." see the whole document ---	1-5,9-11
P,Y	WO,A,95 19978 (LABORATOIRES GLAXO SA) 27 July 1995 cited in the application see page 6 - page 7; claims	1-5,9-11
X	see page 71 - page 74 --- -/--	6-8,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 1996	29. 10. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Klaver, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/EP 96/03024

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NEUROL. URODYN., vol. 13, no. 1, 1994, pages 71-80, XP000568165 F. TRIGO-ROCHA ET AL.: "Intracellular mechanism of penile erection in monkeys." -----	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/EP 96/03024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 3, 4, 9, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The phrase "...another therapeutically active agent..." is insufficienty specific.

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant s protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/03024

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9519978	27-07-95	AU-A-	1574895	08-08-95
		CA-A-	2181377	27-07-95
		FI-A-	962927	19-07-96
		ZA-A-	9500424	27-09-95

Form PCT/ISA/210 (patent family annex) (July 1992)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:

Oren et al.

Serial No. 10/031,464

Filed: April 29, 2002

For: ß-CARBOLINE PHARMACEUTICAL COMPOSITIONS

Attorney Docket No. 29342/36230A

Group Art Unit: 1614

Examiner: Unassigned

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this date

January 13, 2004

James J. Napoli
Registration No. 32,361

STATUS LETTER

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

Sir:

Please advise when an Office Action can be expected in the above-identified application. Kindly note that we have received no response to an application filed April 29, 2002.

Respectfully submitted,

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

By:
James J. Napoli
Registration No. 32,361

January 13, 2004

Access DB# 117416

117715

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Lakshmi Channavajjala Examiner # : 74455 Date: 3-22-04

Art Unit: 1615 Phone Number 30 2-0591 Serial Number: 10/031,464

Mail Box and Bldg/Room Location: REM 4C83 (REM 4C70) Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Beta-carboline ~~formulation~~ pharmaceutical Compositi

Inventors (please provide full names): Peter Oxen, Neil Anderson, Martha Kraft

Earliest Priority Filing Date: natl stage of PCT filed 4/26/00, Prov (8/3/99)

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

(1) Please perform a search of the compound of claim 1.

(2) Please search for a tablet & a capsule formulation comprising the compound of cl. 1 or Beta-carboline carbolines compds.

Thanks

L. Channavajjala

RECEIVED MAR 22 2004 TECH CENTER (ST10)

****

STAFF USE ONLY

Searcher: _____

Searcher Phone #: _____

Searcher Location: _____

Date Searcher Picked Up: _____

Date Completed: _____

Searcher Prep & Review Time: _____

Clerical Prep Time: _____

Online Time: _____

Type of Search

NA Sequence (#)_____

AA Sequence (#)_____

Structure (#) _____

Bibliographic _____

Litigation _____

Fulltext _____

Patent Family _____

Other _____

Vendors and cost where applicable

STN _____

Dialog _____

Questel/Orbit _____

Dr.Link _____

Lexis/Nexis _____

Sequence Systems _____

WWW/Internet _____

Other (specify) _____

PTO-1590 (8-01)

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=> d his ful

     FILE 'HCAPLUS' ENTERED AT 19:05:47 ON 24 MAR 2004
                E OREN PETER/AU
L1            2 SEA ABB=ON  ("OREN PAL ERIC"/AU OR "OREN PAUL E"/AU)
                E ANDERSON NEIL R/AU
L2           17 SEA ABB=ON  ("ANDERSON NEIL R"/AU OR "ANDERSON NEIL ROBERT"/AU)

                E KRAL, MARTHA A/AU
                E KRAL MARTHA A/AU
L3            3 SEA ABB=ON  "KRAL MARTHA A"/AU
L4            0 SEA ABB=ON  L1 AND L2 AND L3
L5           20 SEA ABB=ON  L1 OR L2 OR L3
L6            3 SEA ABB=ON  L5 AND ?CARBOLINE?

     FILE 'REGISTRY' ENTERED AT 19:07:19 ON 24 MAR 2004
L7            8 SEA ABB=ON  (121548-04-7/BI OR 156259-68-6/BI OR 171596-29-5/BI
                  OR 244-63-3/BI OR 25322-68-3/BI OR 31692-85-0/BI OR 57-55-6/BI
                  OR 9003-39-8/BI)

     FILE 'HCAPLUS' ENTERED AT 19:07:30 ON 24 MAR 2004
L8            3 SEA ABB=ON  L6 AND L7

     FILE 'REGISTRY' ENTERED AT 19:14:42 ON 24 MAR 2004
L9            1 SEA ABB=ON  171596-29-5
L10           1 SEA ABB=ON  171596-29-5 OR ?TADALAFIL? OR ?CIALIS?

     FILE 'HCAPLUS' ENTERED AT 19:16:12 ON 24 MAR 2004
                S 171596-29-5/REG# OR ?TADALAFIL? OR ?CIALIS?

     FILE 'REGISTRY' ENTERED AT 19:16:16 ON 24 MAR 2004
L11           1 SEA ABB=ON  171596-29-5/RN
L12           1 SEA ABB=ON  171596-29-5/RN

     FILE 'HCAPLUS' ENTERED AT 19:17:08 ON 24 MAR 2004
L13          82 SEA ABB=ON  L12
L14        6082 SEA ABB=ON  L13 OR ?TADALAFIL? OR ?CIALIS?

     FILE 'REGISTRY' ENTERED AT 19:17:57 ON 24 MAR 2004
                E BETA-CARBONILE/CN
                E BETA CARBONILE/CN
                E BETA CARBOLINE/CN
                E CARBOLINE/CN
L15           2 SEA ABB=ON  CARBOLINE/CN
                E CARBONILE/CN
L16           1 SEA ABB=ON  CARBONIL/CN

     FILE 'HCAPLUS' ENTERED AT 19:22:02 ON 24 MAR 2004
L17         125 SEA ABB=ON  (L14 OR (B OR ?BETA?)(W)?CARBOLIN?) AND (?TABLET?
                  OR ?CAPSUL? OR ?DRUG?(W)?DELIV?)
L18           5 SEA ABB=ON  L17 AND (?MICROCRYST?(W)?CELLULOS? OR ?WETT?(W)?AGE
                  NT?)
L19          16 SEA ABB=ON  L17 AND SEX?(W)?FUNCT?
L20          20 SEA ABB=ON  L18 OR L19

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT
     19:27:17 ON 24 MAR 2004
L21          10 SEA ABB=ON  L20
L22           9 DUP REMOV L21 (1 DUPLICATE REMOVED)
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Inventor search – attached

requested compd – see attached display.

20 cits from CA Plus

9 cits from other database

* I used this term from claim 26 because there were so few (5) for L18

Please let me know if you need further work on this search.

Display requested compound


```
=> d l12

L12  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   171596-29-5  REGISTRY
CN   Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-
     2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-
     2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-trans)-
OTHER NAMES:
CN   (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-
     methylenedioxyphenyl)pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione
CN   Cialis
CN   GF 196960
CN   IC 351
CN   ICOS 351
CN   Tadalafil
FS   STEREOSEARCH
DR   240822-07-5, 282541-36-0
MF   C22 H19 N3 O4
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB,
       CHEMCATS, CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*,
       PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.  Rotation (+).
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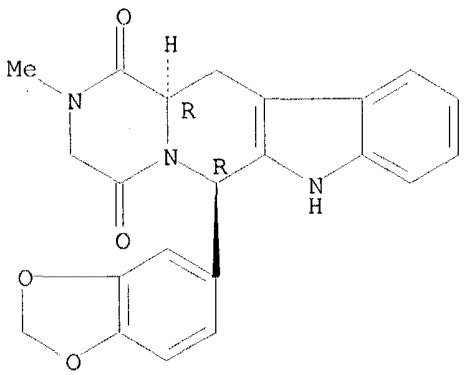


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

              81 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
              82 REFERENCES IN FILE CAPLUS (1907 TO DATE)
ED   Entered STN:  21 Dec 1995
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L12           1 SEA FILE=REGISTRY ABB=ON  171596-29-5/RN
L13          82 SEA FILE=HCAPLUS ABB=ON  L12
L14        6082 SEA FILE=HCAPLUS ABB=ON  L13 OR ?TADALAFIL? OR ?CIALIS?
L17         125 SEA FILE=HCAPLUS ABB=ON  (L14 OR (B OR ?BETA?)(W)?CARBOLIN?)
                AND (?TABLET? OR ?CAPSUL? OR ?DRUG?(W)?DELIV?)
L18           5 SEA FILE=HCAPLUS ABB=ON  L17 AND (?MICROCRYST?(W)?CELLULOS? OR
                ?WETT?(W)?AGENT?)
L19          16 SEA FILE=HCAPLUS ABB=ON  L17 AND SEX?(W)?FUNCT?
L20          20 SEA FILE=HCAPLUS ABB=ON  L18 OR L19

=> d ibib abs hitstr l20 1-20

L20  ANSWER 1 OF 20  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:120699  HCAPLUS
DOCUMENT NUMBER:          140:169665
TITLE:                    New sexual-dysfunction
                          -compound-containing rapid-onset pharmaceutical
                          formulations comprising cocoa powder and use thereof
INVENTOR(S):              Lindberg, Nils-olof; Lindell, Katarina; Thyresson,
                          Kristina; Martino, Alice C.
PATENT ASSIGNEE(S):       Pharmacia Ab, Swed.
SOURCE:                   PCT Int. Appl., 28 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 2004012702      A1   20040212      WO 2003-SE1022   20030618
         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, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
             UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
             NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
             GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                  SE 2002-2365     A  20020805
OTHER SOURCE(S):          MARPAT 140:169665
AB   A sexual-dysfunction-compound-containing a rapid-onset
     pharmaceutical composition that comprises cocoa powder, process for
manufacturing the
     composition and use of the composition in sexual dysfunction
     therapy.
IT   171596-29-5, Tadalafil
     RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical
     process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological
     study); PROC (Process); USES (Uses)
        (new sexual-dysfunction-compound-containing rapid-onset
        pharmaceutical formulations comprising cocoa powder and use thereof)
RN   171596-29-5  HCAPLUS
CN   Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-
     2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI)  (CA INDEX NAME)
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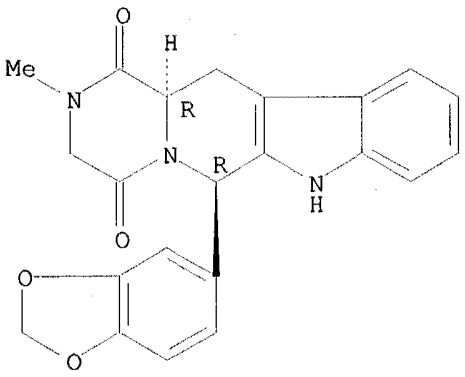
Absolute stereochemistry. Rotation (+).



L20 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:60144 HCAPLUS
DOCUMENT NUMBER: 140:117359
TITLE: Treatment of female **sexual dysfunction** with phosphodiesterase inhibitors
INVENTOR(S): Place, Virgil A.; Wilson, Leland F.; Doherty, Paul C.; Hanamoto, Mark S.; Spivack, Alfred P.; Gesundheit, Neil; Bennett, Sean R.; Doherty, Jane
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S. Ser. No. 499,959.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004014761	A1	20040122	US 2002-279039	20021022
US 5877216	A	19990302	US 1997-959064	19971028
US 6469016	B1	20021022	US 2000-499959	20000208

PRIORITY APPLN. INFO.: US 1997-959057 B2 19971028
US 1997-959064 A2 19971028
US 1998-181316 B3 19981027
US 2000-499959 A2 20000208

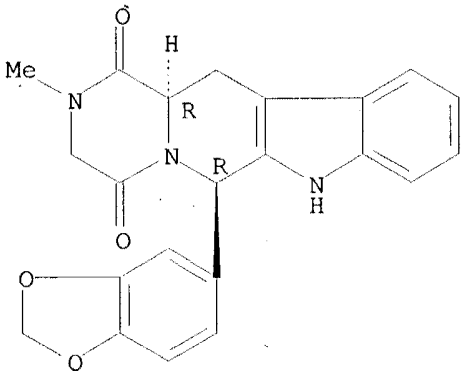
AB A topical pharmaceutical composition is provided for the treatment of female **sexual dysfunction**, wherein the composition is formulated so as to contain a therapeutically effective amount of a phosphodiesterase inhibitor and a pharmaceutically acceptable carrier for topical administration. The phosphodiesterase inhibitor is generally selected from Type III, Type IV, Type V, and nonspecific phosphodiesterase inhibitors. Examples of cream and suppository formulations of sildenafil, **tadalafil** and TA-1790 are given.

IT **171596-29-5, Tadalafil**
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(phosphodiesterase inhibitors for treatment of female **sexual dysfunction**)

RN 171596-29-5 HCAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:818141 HCAPLUS
DOCUMENT NUMBER: 139:312448
TITLE: Methods of treating medication-, substance-, disease-, and other medical condition-related **sexual dysfunction**
INVENTOR(S): Shapira, Nathan Andrew
PATENT ASSIGNEE(S): University of Florida, USA
SOURCE: U.S. Pat. Appl. Publ., 12 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003195186	A1	20031016	US 2003-411644	20030410
WO 2003086372	A2	20031023	WO 2003-US10994	20030410

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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-371666P P 20020410

AB Many males and females experience **sexual dysfunction** either caused or made worse by medications, other substances, diseases, and other medical conditions. Currently, there is need for addnl. treatment alternatives for these patients' **sexual dysfunction**. The subject invention provides a novel treatment for these individuals with **sexual dysfunction** by inhibiting the enzyme that breaks down acetylcholine (a compound that helps modulate normal **sexual function**) and elevates acetylcholine levels in the body. The acetylcholinesterase inhibitor is

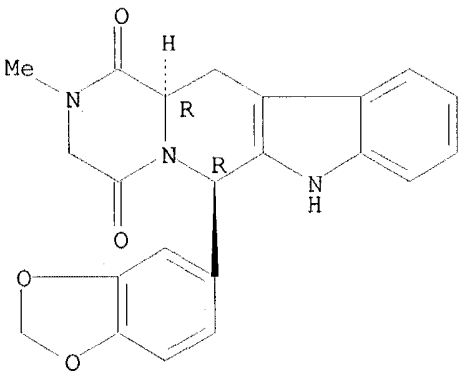
selected from the group consisting of donepezil, galantamine, tacrine, eptastigmine, physostigmine, rivastigmine, metrifonate, neostigmine, huperzine A, and combinations thereof.

IT **171596-29-5, Tadalafil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetylcholinesterase inhibitor in combination with other actives for treatment of **sexual dysfunction**)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:419328 HCAPLUS
DOCUMENT NUMBER: 139:357661
TITLE: The etiology of erectile dysfunction and mechanisms by which drugs improve erection
AUTHOR(S): Galle, Gunter; Trummer, Harald
CORPORATE SOURCE: Department of Urology, Karl-Franzens University of Graz, Austria
SOURCE: Drugs of Today (2003), 39(3), 193-201
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Following the National Institutes of Health (NIH) consensus conference in 1988, erectile dysfunction is defined as the consistent inability to maintain a penile erection sufficient for adequate sexual relations. The advances in basic and clin. research during the last two decades have led to the development of several new treatment options for erectile dysfunction, including new pharmacol. agents for intracavernosal, intraurethral and oral use. The recent advent of medical therapy and the poor results of long-term follow-up in reconstructive vascular surgery, have significantly modified the medical management of this disorder. Discussion of erectile dysfunction has increased, information about erectile dysfunction is increasingly available, training in erectile dysfunction was improved and last, but not least, the number of patients seeking help for erectile dysfunction is growing, because satisfactory **sexual function** is an important part of a couple's healthy relationship and ongoing quality of life.

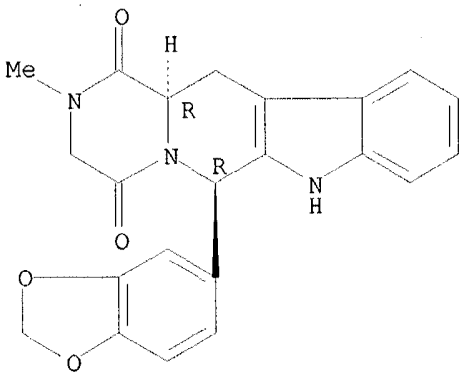
IT **171596-29-5, Tadalafil**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drugs- anr other factors-induced erectile dysfunction and mechanisms by which drugs improve erection)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:792003 HCAPLUS
DOCUMENT NUMBER: 137:299922
TITLE: Nasal spray compositions containing cGMP-PDE inhibitors and local anesthetics for the treatment of male erectile disfunction
INVENTOR(S): Serno, Peter; Ohm, Andreas; Barth, Wolfgang; Bauer, Richard-Josef; Siefert, Hans-Martin; Zimmer, Dieter
PATENT ASSIGNEE(S): Bayer AG, Germany
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10118305	A1	20021017	DE 2001-10118305	20010412
WO 2002083108	A2	20021024	WO 2002-EP3977	20020410
WO 2002083108	A3	20030410		

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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

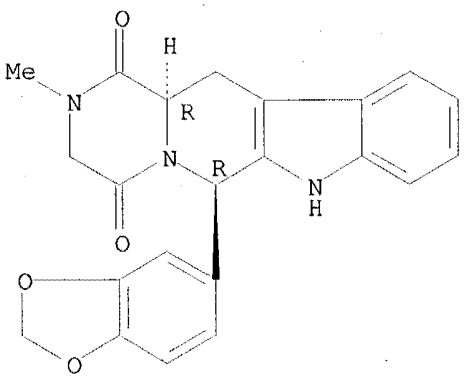
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1383486	A2	20040128	EP 2002-761908	20020410

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: DE 2001-10118305 A 20010412
WO 2002-EP3977 W 20020410
OTHER SOURCE(S): MARPAT 137:299922
AB The present invention concerns compns. for nasal application of cGMP-PDE inhibitors, in particular of PDE5-inhibitors, and local anesthetics; local anesthetics is not benzylalc. The compns. further contain antioxidants, surfactants, stabilizers, **wetting agents**, etc.; nasal sprays and powder inhalants are claimed. Thus a powder composition contained (kg): Sildenafil citrate, micronized 25.0; lidocaine hydrochloride 10.0; lactose 65.0. The homogenized mixture was filled in aliquots of 20 mg into inhaler vials.
IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nasal compns. containing cGMP-PDE inhibitors and local anesthetics for treatment of male erectile disfunction)
RN 171596-29-5 HCAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:241329 HCAPLUS
DOCUMENT NUMBER: 136:284433
TITLE: Administration of phosphodiesterase inhibitors for the treatment of premature ejaculation
INVENTOR(S): Wilson, Leland F.; Doherty, Paul C.; Place, Virgil A.; Smith, William L.; Abdel-Hamid, Abdou Ali Ibrahim Aboubakr
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 467,094.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002037828	A1	20020328	US 2001-888250	20010621
US 6403597	B2	20020611		
US 6037346	A	20000314	US 1998-181070	19981027

US 6548490 B1 20030415 US 1999-467094 19991210
WO 2003000343 A2 20030103 WO 2002-US9415 20020325
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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1997-958816 B2 19971028
US 1998-181070 A2 19981027
US 1999-467094 A2 19991210
US 2001-888250 A 20010621

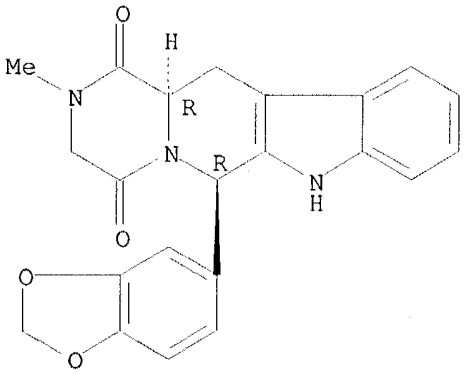
AB A method is provided for treatment of premature ejaculation by administration of a phosphodiesterase inhibitor, e.g., an inhibitor of a Type III, Type IV, or Type V phosphodiesterase. In a preferred embodiment, administration is on as "as needed" basis, i.e., the drug is administered immediately or several hours prior to sexual activity. Pharmaceutical formulations and packaged kits are also provided. Zaprinast 1.0, mannitol 1.0, **microcryst. cellulose** 2.0, and magnesium stearate 10 mg are blended in a suitable mixer and then compressed into sublingual **tablets**. Each sublingual **tablet** contains 10 mg zaprinast.

IT **171596-29-5**, GF 196960
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GF 196960; administration of phosphodiesterase inhibitors for treatment of premature ejaculation)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:51273 HCAPLUS
DOCUMENT NUMBER: 136:96099
TITLE: Treatment of male **sexual dysfunction**
INVENTOR(S): Naylor, Alasdair Mark; Van der Graaf, Pieter Hadewijn; Wayman, Christopher Peter
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002003995	A2	20020117	WO 2001-IB1187	20010702
WO 2002003995	A3	20020418		
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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002052370	A1	20020502	US 2001-893585	20010628
EP 1296687	A2	20030402	EP 2001-947709	20010702
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004502735	T2	20040129	JP 2002-508449	20010702

PRIORITY APPLN. INFO.:

GB 2000-16684	A	20000706
GB 2000-30647	A	20001215
GB 2001-6167	A	20010313
GB 2001-8483	A	20010404
US 2000-219100P	P	20000718
GB 2001-1584	A	20010122
US 2001-274957P	P	20010312
WO 2001-IB1187	W	20010702

OTHER SOURCE(S): MARPAT 136:96099

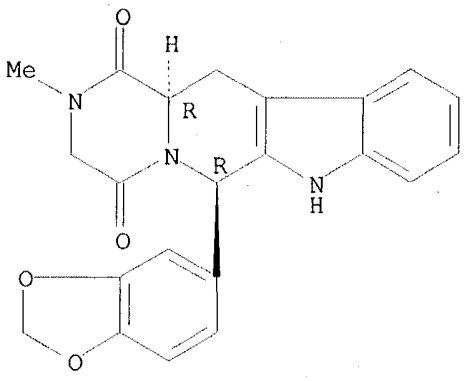
AB The present invention relates to the use of neutral endopeptidase inhibitors (NEPi) and a combination of NEPi and phosphodiesterase type (PDE5) inhibitor for the treatment of male **sexual dysfunction**, in particular MED.

IT **171596-29-5**, IC-351
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of male **sexual dysfunction** using neutral endopeptidase inhibitors and their combination with phosphodiesterase type 5 inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:924320 HCAPLUS
DOCUMENT NUMBER: 136:31728
TITLE: Daily treatment for erectile dysfunction using a phosphodiesterase 5 (PDE5) inhibitor
INVENTOR(S): Whitaker, John S.; Saenz de Tejada, Inigo; Ferguson, Kenneth M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 558,911.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001053780	A1	20011220	US 2001-834442	20010413
EP 1173181	A2	20020123	EP 2000-926367	20000426
EP 1173181	B1	20031015		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6451807	B1	20020917	US 2000-558911	20000426
JP 2002543116	T2	20021217	JP 2000-614984	20000426
BR 2000010181	A	20030225	BR 2000-10181	20000426
NZ 514882	A	20030829	NZ 2000-514882	20000426
AT 251908	E	20031115	AT 2000-926367	20000426
HR 2001000778	A1	20021231	HR 2001-778	20011023
NO 2001005275	A	20011206	NO 2001-5275	20011029
US 2003100478	A1	20030529	US 2002-198903	20020719
US 2003144296	A1	20030731	US 2003-341664	20030114

PRIORITY APPLN. INFO.: US 1999-132036P P 19990430
US 2000-558911 A2 20000426
WO 2000-US11129 W 20000426
US 2001-834442 A3 20010413

AB The invention provides phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manufacture In particular, the invention provides potent inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that, when incorporated into a pharmaceutical product at about 1-10 mg unit dosage, are useful for the treatment of **sexual dysfunction** by daily administration of the PDE5 inhibitor. The articles of manufacture

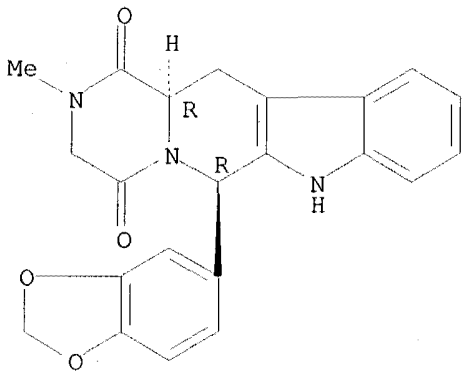
described are characterized by PDE5 inhibition, and accordingly, provide a benefit in therapeutic areas where inhibition of PDE5 is desired, especially erectile dysfunction, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes and with an improvement of vascular conditioning.

IT **171596-29-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase 5 inhibitor for daily treatment for erectile dysfunction)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:916407 HCAPLUS
DOCUMENT NUMBER: 136:53755
TITLE: Synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of **sexual dysfunction**
INVENTOR(S): Garvey, David S.; Saenz de Tejada, Inigo; Earl, Richard A.; Khanapure, Subhash P.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: U.S., 117 pp., Cont.-in-part of U.S. 5,958,926.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6331543	B1	20011218	US 1999-387727	19990901
US 5874437	A	19990223	US 1996-740764	19961101
WO 9819672	A1	19980514	WO 1997-US19870	19971031
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5958926	A	19990928	US 1998-145142	19980901
US 2002019405	A1	20020214	US 2001-941691	20010830
US 6462044	B2	20021008		
US 2003023087	A1	20030130	US 2002-216886	20020813

PRIORITY APPLN. INFO.: US 1996-740764 A2 19961101

WO 1997-US19870 A2 19971031
US 1998-145142 A2 19980901
US 1999-387727 A1 19990901
US 2001-941691 A3 20010830

OTHER SOURCE(S): MARPAT 136:53755

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

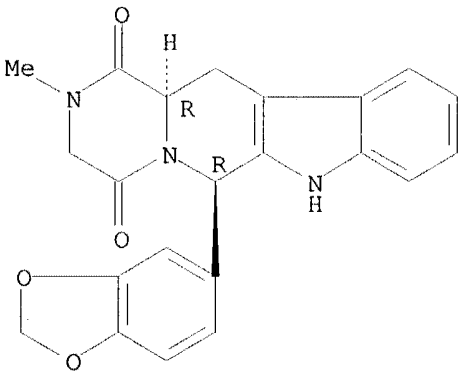
AB Compds. I-V, derivs. thereof, and certain substituted Ph and phthalzaine derivs. were claimed [D2 = H, alkyl, D; D = NO, NO2, alkyl, acyl, phosphoryl, silyl, etc.; A1-3 comprise the other subunits of a 5- or 6-membered monocyclic aromatic ring; R8 = H, (halo)alkyl; p = 1-10; R24 = H, cyclohexyl, piperidinyl, etc., with the proviso that at least one of A1-3, J, or R24 contains T-Q or D; T = bond, O, S(O), amino; Q = NO, NO2; D1 = D or H; R37 = (hetero)aryl; R38 = H, halo, alkyl; G1 = alkyl, alkenyl or is part of a ring fused to the piperidine moiety of III; G4 = O, S; R40 = H, alkyl, haloalkyl, halo, etc.; R41 = alkyl, hydroxyalkyl, alkylcarboxy, etc.; R42 = aryl, alkylaryl, alkyloxyaryl; T1 = alkyl, oxyalkyl, thioalkyl, aminoalkyl]. Two synthetic examples were provided. E.g., the S-nitroso derivative of the 3-mercapto-3-methylbutyric acid ester of dipyridamole (VI) was prepared in 4 steps from dipyridamole in 3.5% overall yield. VI at doses of 10 and 30 μM was more efficacious in relaxing phenylephrine-induced tissue contraction than was the known phosphodiesterase inhibitor, dipyridamole. The present invention describes novel (nitrosated/nitrosylated) phosphodiesterase inhibitors, and compns. containing at least one (nitrosated/nitrosylated) phosphodiesterase inhibitor, and, optionally, one or more compds. that donate, transfer or release NO, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of NO, or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for treating or preventing **sexual dysfunctions** in males and females, for enhancing sexual responses in males and females, and for treating or preventing diseases induced by the increased metabolism of cGMP, such as hypertension, pulmonary hypertension, etc.

IT **171596-29-5D**, ICOS 351, nitroso derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of **sexual dysfunction**)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:798055 HCAPLUS
DOCUMENT NUMBER: 135:339295
TITLE: Daily treatment for erectile dysfunction using a phosphodiesterase 5 (PDE5) inhibitor
INVENTOR(S): Whitaker, John S.; Saenz de Tejada, Inigo; Ferguson, Kenneth M.
PATENT ASSIGNEE(S): Lilly Icos LLC, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080860	A2	20011101	WO 2001-US12512	20010413
WO 2001080860	A3	20020606		
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, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6451807	B1	20020917	US 2000-558911	20000426
EP 1276481	A2	20030122	EP 2001-927133	20010413
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001010373	A	20030218	BR 2001-10373	20010413
JP 2003531174	T2	20031021	JP 2001-577959	20010413
NO 2002005138	A	20021216	NO 2002-5138	20021025
ZA 2002008776	A	20030603	ZA 2002-8776	20021030

PRIORITY APPLN. INFO.:
US 2000-558911 A 20000426
US 1999-132036P P 19990430
WO 2001-US12512 W 20010413

AB The invention relates to phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manufacture In particular, the

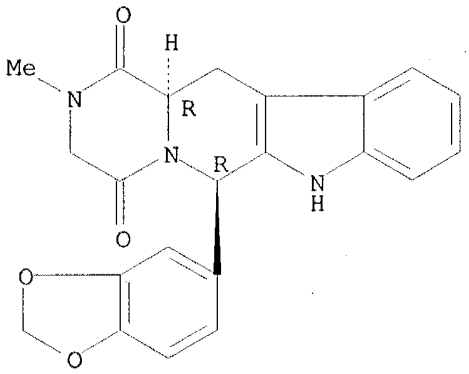
invention relates to potent inhibitors of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase type 5 (PDE5) that, when incorporated into a pharmaceutical product at about 1 to about 10 mg unit dosage, are useful for the treatment of **sexual dysfunction** by daily administration of the PDE5 inhibitor. The articles of manufacture are characterized by PDE5 inhibition, and accordingly provide a benefit in therapeutic areas where inhibition of PDE5 is desired, especially erectile dysfunction, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes and with an improvement of vascular conditioning.

IT **171596-29-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase 5 inhibitor for daily treatment for **sexual dysfunction**)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:713326 HCAPLUS
DOCUMENT NUMBER: 135:272990
TITLE: Preparation of piperazinylcarbonylaminomethylcarbonylpiperidines as melanocortin-4 receptor agonists
INVENTOR(S): Palucki, Brenda L.; Barakat, Khaled J.; Guo, Liangqin; Lai, Yingjie; Nargund, Ravi P.; Park, Min K.; Pollard, Patrick G.; Sebhat, Iyassu K.; Ye, Zhixiong
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070708	A1	20010927	WO 2001-US8935	20010320

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, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT,

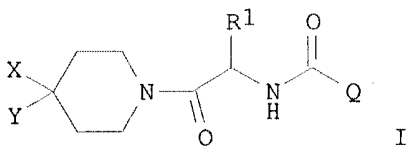
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002019523	A1	20020214	US 2001-812965	20010320
US 6458790	B2	20021001		
EP 1268449	A1	20030102	EP 2001-922501	20010320
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003528088	T2	20030924	JP 2001-568918	20010320

PRIORITY APPLN. INFO.:
US 2000-191442P P 20000323
US 2000-242265P P 20001020
WO 2001-US8935 W 20010320

OTHER SOURCE(S): MARPAT 135:272990

GI



I

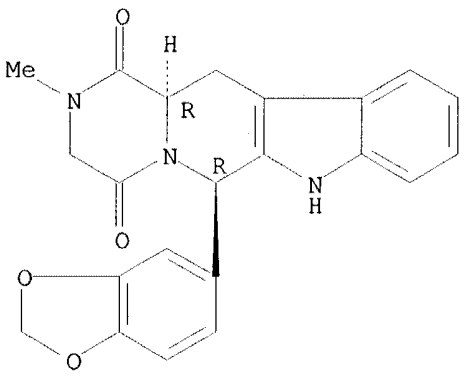
AB Title compds. [I; Q = (substituted) (fused) piperazinyl, morpholinyl, thiomorpholinyl; R1 = H, alkyl, (substituted) cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), etc.; X = (substituted) alkyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), cyano(alkyl), aminosulfonyl(alkyl), etc.; Y = H, alkyl, cycloalkyl(alkyl), (substituted) aryl(alkyl), heterocyclyl(alkyl), heteroaryl(alkyl)], were prepared as melanocortin-4 receptor (MC-4R) agonists. Thus, **capsule** formulations containing title compound (II) were prepared Representative I activated MC-4R with IC50<1 μM. I are claimed for the treatment of obesity, diabetes, and **sexual dysfunction** including erectile dysfunction and female **sexual dysfunction**.

IT **171596-29-5**, IC-351
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; preparation of piperazinylcarbonylaminomethylcarbonylpiperidines as melanocortin-4 receptor agonists)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:559496 HCAPLUS
DOCUMENT NUMBER: 135:117266
TITLE: Treatment of **sexual function** disorders with phosphodiesterase 4 inhibitors as monotherapy or in combination with other phosphodiesterase inhibitors or adenylate cyclase activators
PATENT ASSIGNEE(S): Stief, Christian, Germany
SOURCE: Ger. Offen., 4 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10004289	A1	20010802	DE 2000-10004289	20000201

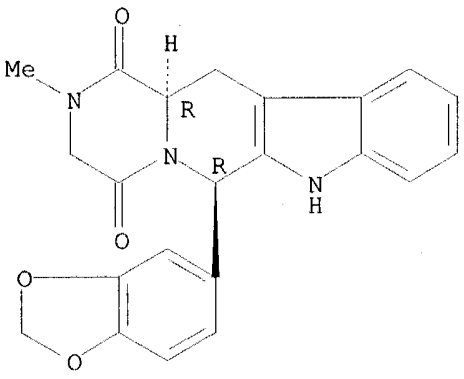
PRIORITY APPLN. INFO.: DE 2000-10004289 20000201

AB The invention provides a medicament containing a phosphodiesterase 4 inhibitor as monotherapy or in combination with other phosphodiesterase inhibitors or adenylate cyclase activators for the treatment of s **sexual function** disorders.

IT **171596-29-5**, IC 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase 4 inhibitors as monotherapy or in combination with other phosphodiesterase inhibitors or adenylate cyclase activators for treatment of **sexual function** disorders)

RN 171596-29-5 HCAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:541505 HCAPLUS
DOCUMENT NUMBER: 135:132460
TITLE: Treatment of **sexual function** disorders with guanylate cyclase activators, optionally in combination with phosphodiesterase inhibitors
INVENTOR(S): Stief, Christian; Magerl, Hans-Jurgen; Kuthe, Andrea; Uckert, Stefan; Becker, Armin; Farssmann, Wolf Georg; Jones, Udo
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 6 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10002200	A1	20010726	DE 2000-10002200	20000119

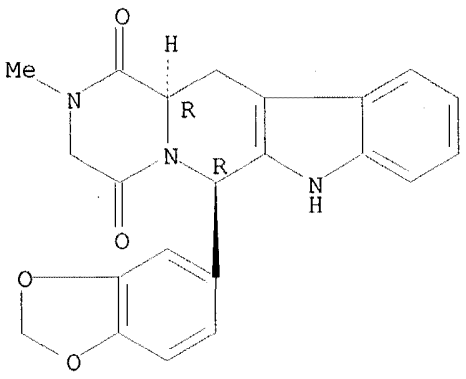
PRIORITY APPLN. INFO.: DE 2000-10002200 20000119

AB Medicaments containing activators of guanylate cyclase and their variants, individually or in combination with phosphodiesterase inhibitors, are provided for the treatment of **sexual function** disorders. e.g. erectile dysfunction.

IT **171596-29-5**, IC 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(guanylate cyclase activators, optionally in combination with phosphodiesterase inhibitors, for treatment of **sexual function** disorders)

RN 171596-29-5 HCAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:100983 HCAPLUS
DOCUMENT NUMBER: 134:152655
TITLE: Pharmaceutical compositions containing **.beta.-carboline** drugs
INVENTOR(S): Anderson, Neil R.; Hartauer, Kerry J.; Kral, Martha A.; Stephenson, Gregory A.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008688	A2	20010208	WO 2000-US20981	20000801
WO 2001008688	A3	20010816		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000012901	A	20020416	BR 2000-12901	20000801
EP 1200092	A2	20020502	EP 2000-952371	20000801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505510	T2	20030212	JP 2001-513418	20000801
NZ 516613	A	20030829	NZ 2000-516613	20000801
ZA 2002000825	A	20030207	ZA 2002-825	20020130
NO 2002000531	A	20020403	NO 2002-531	20020201

PRIORITY APPLN. INFO.: US 1999-147048P P 19990803
WO 2000-US20981 W 20000801

AB Pharmaceutical compns. containing β **-carboline** drugs and pharmaceutically acceptable salts and solvates thereof, wherein the drug is in free particulate form, is disclosed. A **tablet** contained a β **-carboline** drug 10.00, lactose monohydrate 153.80, spray dried lactose monohydrate 25.00, hydroxypropyl

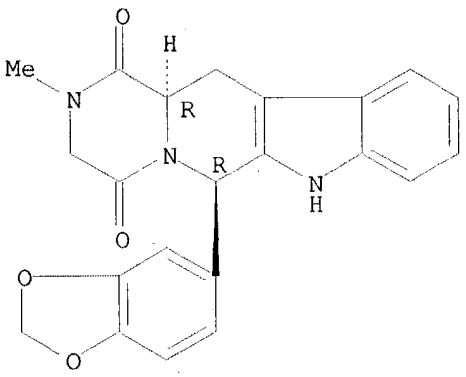
cellulose 4.00, croscarmellose sodium 16.00, hydroxypropyl cellulose 1.75, sodium lauryl sulfate 0.70, **microcryst. cellulose** 37.50, and magnesium stearate 1.25 mg. The improvement in bioavailability of the drug was demonstrated in humans.

IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing β **-carboline** drugs)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:100982 HCAPLUS
DOCUMENT NUMBER: 134:152654
TITLE: β **-Carboline** pharmaceutical compositions
INVENTOR(S): Anderson, Neil R.; Gullapalli, Rampurna P.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008687	A1	20010208	WO 2000-US11136	20000426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1200091	A1	20020502	EP 2000-926371	20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
ZA 2002000823	A	20030204	ZA 2002-823	20020130

PRIORITY APPLN. INFO.: US 1999-146924P P 19990803
WO 2000-US11136 W 20000426

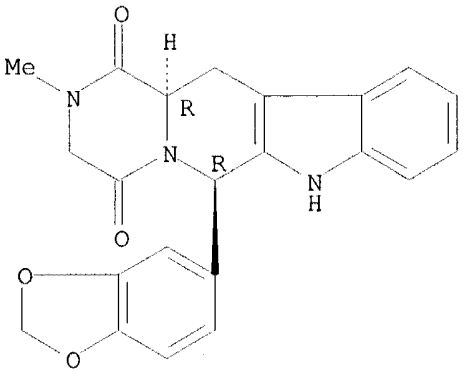
AB β -**Carboline** soft **capsules** contains a solution or suspension of a PDE5 inhibitor, and are useful for treating **sexual dysfunction**. Thus, a formulation contained a . **beta.-carboline** 25.0, Capmul MCM 177.5, Gelucire 44/14 177.5, and propylene glycol 20.0 mg/**capsule**. In the phys. study of the above **capsule** formulation, no sedimentation was observed after storage at 4° for 120 days.

IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β -**carboline** pharmaceutical compns.)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:100981 HCAPLUS
DOCUMENT NUMBER: 134:152653
TITLE: β -**Carboline** pharmaceutical compositions containing cellulose
INVENTOR(S): Oren, Peter L.; Anderson, Neil R.; Kral, Martha A.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008686	A1	20010208	WO 2000-US11130	20000426

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

BR 2000012863	A	20020416	BR 2000-12863		20000426
EP 1200090	A1	20020502	EP 2000-926368		20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
JP 2003505509	T2	20030212	JP 2001-513416		20000426
NZ 516616	A	20030725	NZ 2000-516616		20000426
ZA 2002000823	A	20030204	ZA 2002-823		20020130
NO 2002000532	A	20020326	NO 2002-532		20020201
PRIORITY APPLN. INFO.:			US 1999-146924P	P	19990803
			WO 2000-US11130	W	20000426

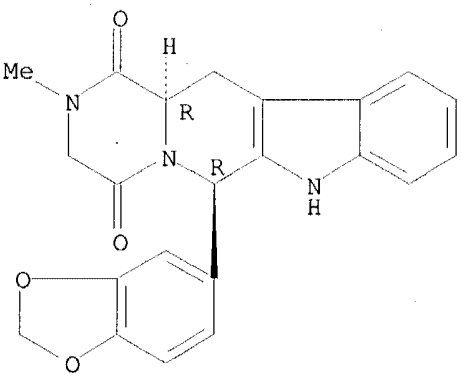
AB β -**Carboline** formulations contain a c-GMP phosphodiesterase inhibitor, a water-soluble diluent, a lubricant, a hydrophilic binder, a disintegrant, and optional **microcryst. cellulose** and/or a **wetting agent**, are useful for treating **sexual dysfunction.** Thus, a **tablet** formulation contained a β -**carboline** 5.00, lactose monohydrate 109.655, lactose monohydrate (spray dried) 17.50, Hydroxypropyl cellulose 4.025, croscarmellose sodium 6.30, SLS 0.49, **microcryst. cellulose** (granular-102) 26.25, croscarmellose sodium 4.90, and Mg stearate 0.88 mg/**tablet.**

IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β -**carboline** pharmaceutical compns. containing cellulose)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2000:686171 HCAPLUS
DOCUMENT NUMBER:	133:271672
TITLE:	Phosphodiesterase inhibitor preparation for treatment of **sexual functional** disorders
PATENT ASSIGNEE(S):	Lilly Icos Llc, USA
SOURCE:	Ger. Gebrauchsmusterschrift, 47 pp. CODEN: GGXXFR
DOCUMENT TYPE:	Patent
LANGUAGE:	German

FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 20007861	U1	20000928	DE 2000-20007861	20000426
NO 2000002097	A	20011026	NO 2000-2097	20000425
ES 2187234	A1	20030516	ES 2000-1055	20000425
CA 2307101	AA	20001030	CA 2000-2307101	20000426
CA 2307101	C	20030128		
FI 2000000976	A	20001030	FI 2000-976	20000426
NL 1015027	A1	20001031	NL 2000-1015027	20000426
NL 1015027	C2	20010214		
SE 2000001518	A	20001031	SE 2000-1518	20000426
ZA 2000002058	A	20001102	ZA 2000-2058	20000426
WO 2000066099	A2	20001109	WO 2000-US11129	20000426
WO 2000066099	A3	20010118		
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10021266	A1	20001116	DE 2000-10021266	20000426
PT 102457	A	20001130	PT 2000-102457	20000426
JP 2000336043	A2	20001205	JP 2000-126472	20000426
FR 2795646	A1	20010105	FR 2000-5296	20000426
FR 2795646	B1	20020816		
GB 2351663	A1	20010110	GB 2000-10199	20000426
LT 4758	B	20010226	LT 2000-35	20000426
LV 12560	B	20010420	LV 2000-56	20000426
CN 1292264	A	20010425	CN 2000-106987	20000426
SI 20361	C	20010430	SI 2000-107	20000426
BE 1012957	A5	20010605	BE 2000-295	20000426
NZ 504163	A	20011130	NZ 2000-504163	20000426
HR 2000000243	A1	20011231	HR 2000-243	20000426
EP 1173181	A2	20020123	EP 2000-926367	20000426
EP 1173181	B1	20031015		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
LU 90569	A2	20020227	LU 2000-90569	20000426
CH 692478	A	20020715	CH 2000-81900	20000426
BR 2000003046	A	20020723	BR 2000-3046	20000426
JP 2002543116	T2	20021217	JP 2000-614984	20000426
BR 2000010181	A	20030225	BR 2000-10181	20000426
NZ 514882	A	20030829	NZ 2000-514882	20000426
SG 98384	A1	20030919	SG 2000-2287	20000426
AT 251908	E	20031115	AT 2000-926367	20000426
HR 2001000778	A1	20021231	HR 2001-778	20011023
NO 2001005275	A	20011206	NO 2001-5275	20011029
ZA 2001008900	A	20030108	ZA 2001-8900	20011029

PRIORITY APPLN. INFO.: US 1999-132036P P 19990430
WO 2000-US11129 W 20000426

AB A formulation for the treatment of **sexual malfunctions** (e.g., erectile dysfunction in men and decreased libido in women) which contains a phosphodiesterase 5 inhibitor with a IC50 of at least 100-fold lower than that with phosphodiesterase 6 as active ingredient, and which

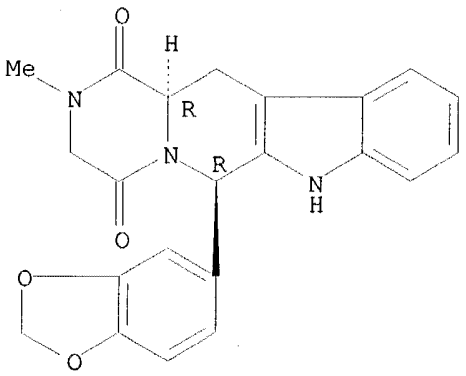
inhibits phosphodiesterase 5 with an IC50 of at least 1000-fold lower than for phosphodiesterase 1c and a IC50 for PDE5 of below 10 nM.

IT **171596-29-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(phosphodiesterase inhibitor preparation for treatment of **sexual functional** disorders)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L20 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:666601 HCAPLUS
DOCUMENT NUMBER: 133:256811
TITLE: Pharmaceutical compositions containing dopamine agonists in combination with nitric oxide donors for treating and/or preventing **sexual dysfunctions**
INVENTOR(S): Garvey, David S.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054773	A1	20000921	WO 2000-US3709	20000310

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-123920P P 19990312
OTHER SOURCE(S): MARPAT 133:256811

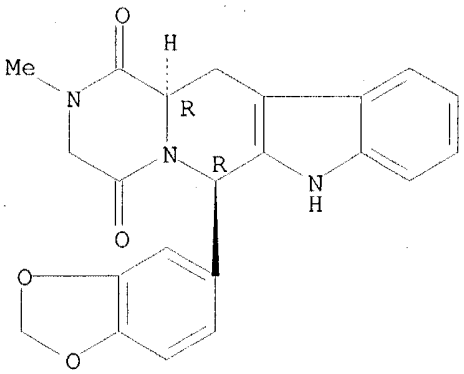
AB The present invention is directed to novel compns. comprising at least one dopamine agonist in combination with at least one nitric oxide donor (i.e. compds. that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase). The novel compns. may optionally comprise at least one therapeutic agent, such as, a vasoactive agent, an antiemetic agent, and mixts. thereof. The dopamine agonist is preferably apomorphine. The present invention is also directed to methods for treating and/or preventing **sexual dysfunctions** and/or enhancing sexual responses in patients. In other embodiments, the present invention is directed to methods treating or preventing neurodegenerative diseases, mitochondrial diseases, spinal cord injury, central or psychostimulant addiction, senile dementia, circulatory disorders, cardiovascular disorders, hyperprolactinemia or myopia. The compds. and/or compns. of the present invention can also be provided in the form of a pharmaceutical kit (no data).

IT **171596-29-5**, Ic 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing dopamine agonists in combination with nitric oxide donors for treating and/or preventing **sexual dysfunctions**)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:753072 HCAPLUS
DOCUMENT NUMBER: 131:346565
TITLE: Combination of phentolamine and cyclic GMP phosphodiesterase inhibitors for the treatment of **sexual dysfunction**
INVENTOR(S): Estok, Thomas Mark
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959584	A1	19991125	WO 1999-US7046	19990517
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9940685	A1	19991206	AU 1999-40685	19990517

PRIORITY APPLN. INFO.:

US 1998-81640	A	19980520
US 1998-82977	A2	19980521
US 1998-106517	A	19980629
WO 1999-US7046	W	19990517

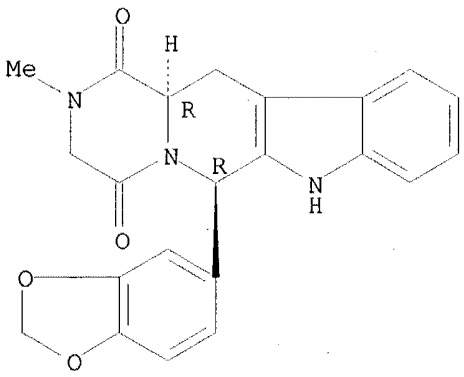
AB A method of treating **sexual dysfunction** comprising administering a therapeutically effective amount of a combination of phentolamine and cGMP PDE inhibitor (e.g. sildenafil), as well as pharmaceutical compns. and kits useful in those methods, are disclosed.

IT **171596-29-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phentolamine and cyclic GMP phosphodiesterase inhibitors for the treatment of **sexual dysfunction**)

RN 171596-29-5 HCAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:240243 HCAPLUS
DOCUMENT NUMBER: 124:333120
TITLE: Tetrahydro-β -**carbolines** with central nervous system activity
INVENTOR(S): Audia, James E.; Droste, James J.; Evrard, Deborah A.; Fludzinski, Pawel; Murdoch, Gwyn L.; Nelson, David L.
PATENT ASSIGNEE(S): Eli Lilly and Co., USA

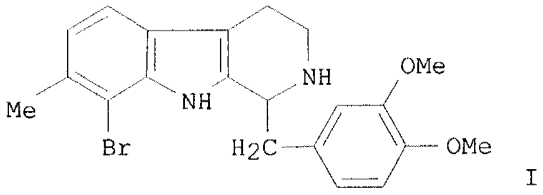
SOURCE: U.S., 50 pp., Cont.-in-part of U.S. Ser. No. 48, 544, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5500431	A	19960319	US 1994-206839	19940311
EP 620222	A2	19941019	EP 1994-302608	19940413
EP 620222	A3	19950412		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
ZA 9402543	A	19951013	ZA 1994-2543	19940413
CA 2160481	AA	19941027	CA 1994-2160481	19940414
WO 9423720	A1	19941027	WO 1994-US4386	19940414
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9467102	A1	19941108	AU 1994-67102	19940414
JP 08509228	T2	19961001	JP 1994-523577	19940414
US 5508284	A	19960416	US 1995-448005	19950523
US 5635528	A	19970603	US 1995-481716	19950607
US 5760051	A	19980602	US 1995-481714	19950607
US 5861425	A	19990119	US 1997-845053	19970418
US 6090945	A	20000718	US 1998-187066	19981105

PRIORITY APPLN. INFO.:
US 1993-48544 B2 19930414
US 1994-206839 A 19940311
WO 1994-US4386 W 19940414
US 1995-481714 A3 19950607
US 1997-845053 A3 19970418

OTHER SOURCE(S): MARPAT 124:333120

GI



I

AB Tetrahydro-β -**carbolines** and their benzo homologs are prepared which show high selective affinity for serotoninergic 5-HT1C receptors and are useful in treatment of disorders associated with 5-HT1C modulation. Tryptamine derivs. with 5-HT2A, 5-HT2B, and/or 5-HT2C receptor-modulating activity are also prepared Thus, 7-methyl-8-bromo-1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-HCl (I-HCl) displaced mesulergine-3H from beef brain 5-HT1C receptors with IC50 = 5.1 nM and displaced ketanserin-3H from 5-HT2 receptors with IC50 >100 nM. I-HCl was prepared from 2-bromo-3-methylaniline by reaction with NaNO2 and SnCl2 to form 2-bromo-3-methylphenylhydrazine-HCl, condensation with 4-chlorobutanal to form 6-methyl-7-bromotryptamine-HCl, and condensation with the azlactone from 3,4-dimethoxybenzaldehyde and

N-acetylglycine. **Capsules** were prepared containing 6-methyl-8-ethyl-1-[(3-bromo-4-chlorophenyl)methyl]-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (Z)-2-butenedioate 20, starch 89, **microcryst . cellulose** 89, and Mg stearate 2 mg.

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=> d que stat l22
L12           1 SEA FILE=REGISTRY ABB=ON  171596-29-5/RN
L13          82 SEA FILE=HCAPLUS ABB=ON  L12
L14        6082 SEA FILE=HCAPLUS ABB=ON  L13 OR ?TADALAFIL? OR ?CIALIS?
L17         125 SEA FILE=HCAPLUS ABB=ON  (L14 OR (B OR ?BETA?)(W)?CARBOLIN?)
                AND (?TABLET? OR ?CAPSUL? OR ?DRUG?(W)?DELIV?)
L18           5 SEA FILE=HCAPLUS ABB=ON  L17 AND (?MICROCRYST?(W)?CELLULOS? OR
                ?WETT?(W)?AGENT?)
L19          16 SEA FILE=HCAPLUS ABB=ON  L17 AND SEX?(W)?FUNCT?
L20          20 SEA FILE=HCAPLUS ABB=ON  L18 OR L19
L21          10 SEA L20
L22           9 DUP REMOV L21 (1 DUPLICATE REMOVED)

=> d ibib abs l22 1-9

L22  ANSWER 1 OF 9  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:   2003179247  EMBASE
TITLE:              The year's new drugs.
AUTHOR:             Graul A.I.
SOURCE:             Drug News and Perspectives, (2003) 16/1 (22-39).
                    ISSN: 0214-0934  CODEN: DNPEED
COUNTRY:            Spain
DOCUMENT TYPE:      Journal; General Review
FILE SEGMENT:       030     Pharmacology
                    036     Health Policy, Economics and Management
                    037     Drug Literature Index
                    038     Adverse Reactions Titles
                    039     Pharmacy
LANGUAGE:           English
SUMMARY LANGUAGE:   English
AB   The United States was the most active market for new product launches (22
     products, 62.5%) in a year that saw 33 new chemical entities and
     biological drugs and two diagnostic agents reach their first markets. The
     most active therapeutic groups were antiinfective, oncolytic and metabolic
     drugs with five launches for each. .COPYRGT. 2003 Prous Science. All
     rights reserved.

L22  ANSWER 2 OF 9  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:   2003366166  EMBASE
TITLE:              Hypogonadism and erectile dysfunction: The role for
                    testosterone therapy.
AUTHOR:             Shabsigh R.
CORPORATE SOURCE:   Dr. R. Shabsigh, Department of Urology, Columbia
                    University, Columbia-Presbyterian Medical Center, 161 Fort
                    Washington Avenue, New York, NY 10032, United States.
                    rs66@columbia.edu
SOURCE:             International Journal of Impotence Research, (2003)
                    15/SUPPL. 4 (S9-S13).
                    Refs: 32
                    ISSN: 0955-9930  CODEN: IJIRFB
COUNTRY:            United Kingdom
DOCUMENT TYPE:      Journal; General Review
FILE SEGMENT:       003     Endocrinology
                    017     Public Health, Social Medicine and Epidemiology
                    028     Urology and Nephrology
                    037     Drug Literature Index
                    038     Adverse Reactions Titles
LANGUAGE:           English
```

SUMMARY LANGUAGE: English

AB The role of low testosterone levels in erectile dysfunction (ED) remains unclear. Both organic and psychogenic factors contribute to ED, with vasculogenic causes being the most common etiology. Approximately 10-20% of patients with ED are diagnosed with hormonal abnormalities. At the physiologic level, two second messenger systems are involved in mediating erections, one involving cyclic adenosine monophosphate (cAMP) and the other involving cyclic guanosine monophosphate (cGMP). PDE5 inhibitors such as sildenafil promote the cGMP pathway, while alprostadil affects the cAMP pathway. Evidence is strong that, in animal systems, testosterone has direct effects on erectile tissue. However, although testosterone clearly has an impact on libido in humans, its effect on penile function is less clear. Evaluation of ED includes medical, sexual, and psychosocial history assessments, as well as laboratory tests to check for diabetes and hormonal abnormalities. Initial interventions should involve correction of potentially reversible causes of ED, such as hypogonadism. First-line therapy for other patients is typically oral PDE5 inhibitors, such as sildenafil, **tadalafil**, or vardenafil. For patients who fail treatment with PDE5 inhibitors, local therapies such as intracavernous alprostadil are highly successful. Recent data also support the success of combination therapy with sildenafil and testosterone. This opens the possibility of other combinations of testosterone and other treatments of ED. The ability to exploit multiple pathways in the physiologic processes leading to erection may help improve therapy for ED.

L22 ANSWER 3 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002378170 EMBASE

TITLE: The potential role of minoxidil in the hair transplantation setting.

AUTHOR: Avram M.R.; Cole J.P.; Gandelman M.; Haber R.; Knudsen R.; Leavitt M.L.; Leonard Jr. R.T.; Puig C.J.; Rose P.T.; Vogel J.E.; Ziering C.L.; Fitzpatrick R.E.

CORPORATE SOURCE: Dr. M.R. Avram, 927 Fifth Ave., New York, NY 10021, United States. info@dravram.com

SOURCE: Dermatologic Surgery, (1 Oct 2002) 28/10 (894-900). Refs: 24
ISSN: 1076-0512 CODEN: DESUFE

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 009 Surgery
013 Dermatology and Venereology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB BACKGROUND. Over the last decade surgical management of hair loss has become an increasingly popular and satisfying procedure for both men and women, as innovations in donor harvesting, graft size, and hairline design have resulted in consistently natural-appearing hair restoration. OBJECTIVE. In addition, a better understanding of the regulation of the hair-growth cycle has led to advances in the pharmacologic treatment of androgenetic alopecia. METHODS. Currently there are two U.S. Food and Drug Administration (FDA)-approved agents that promote hair regrowth: over-the-counter topical minoxidil solution for men and women and prescription oral finasteride **tablets** for men. In October 2001, a group of 11 international experts on hair loss and hair transplantation convened to review the physiology and effects of pharmacologic treatments of hair loss and to discuss the value of administering topical minoxidil

therapy as an adjunct to hair transplantation. RESULTS. This article presents the key findings and consensus points among the participants, including their current use of pharmacologic treatments, strategies for optimal results both pre- and postsurgery, and the importance of realistic patient expectations and compliance. CONCLUSIONS. Based on the surgeons' clinical experience, the use of approved hair regrowth agents in hair transplant patients with viable but suboptimally functioning follicles in the region to be transplanted can increase hair density, speed regrowth in transplanted follicles, and complement the surgical result by slowing down or stopping further hair loss.

L22 ANSWER 4 OF 9 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2002608630 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12365078
TITLE: [**Sexual dysfunction** in treated hypertensive patients. Results of a national survey]. Troubles de la sexualite chez les hypertendus traites. Resultats d'une enquete nationale.
AUTHOR: Hanon O; Mounier-Vehier Cl; Fauvel J P; Marquand A; Jaboureck O; Justin E P; Kearney-Schwartz A; Girerd X
CORPORATE SOURCE: Service de medecine interne, hopital Broussais, 96, rue Didot, 75014 Paris.
SOURCE: Archives des maladies du coeur et des vaisseaux, (2002 Jul-Aug) 95 (7-8) 673-7.
Journal code: 0406011. ISSN: 0003-9683.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021008
Last Updated on STN: 20021030
Entered Medline: 20021029

AB OBJECTIVES: To evaluate, using an self-administered questionnaire, the characteristics of **sexual function** in treated hypertensives. METHODS: In 459 hypertensive subjects, aged of 59 +/- 12 years, living in France and referred to hypertension **specialists** , a self-administered questionnaire evaluating quality of life and antihypertensive treatment was given before the consultation. Several questions focused on the quality of **sexual function** since the last 12 months (interest for sexuality, sexual pleasure, quality of erection). Details on antihypertensive treatments and cardiovascular characteristics were obtained from medical records. Antihypertensive treatments were prescribed since more than 10 years for 39% of subjects, since 5-10 years for 25%, since 1-5 years for 26%, and since less than 1 year for 10%. RESULTS: In this population of treated hypertensives, blood pressure level was higher in men than in women (145 +/- 22/86 +/- 13 vs 135 +/- 25/76 +/- 15; $p < 0.01$). In the questionnaire, the section with **sexual function** questions was filled out extensively in 92% of men (248/268), but only in 74% of women (142/191). Sexual disturbance was declared by 38% of cases (148/390), but rate was significantly higher in men as compared to women (49% vs 18%; $p < 0.01$). In men, these modifications were characterised by an interest for sexuality decreased for 58%, unchanged for 41% and increased for 1%. Sexual pleasure was decreased for 49%, unchanged for 50%, and increased for 1%. Quality of erection was modified in 45%. The erections were less frequent for 31%, less durable for 19% and impossible for 11%. In women, interest for sexuality was decreased for 41% and unchanged for 59%, sexual pleasure was decreased for 34% and unchanged for 66%. Logistic regression analysis indicates that gender ($p < 0.001$), greater number of

antihypertensive **tablets** ($p < 0.01$), prescription of diuretics ($p = 0.03$) and presence of coronaropathy ($p = 0.01$) were independent determinants for sexual disturbance in treated hypertensives. CONCLUSION: This study indicates that sexual disturbance is declared by 38% of patients treated for hypertension. Because complaints are more frequent in men, treated with multiple medications including a diuretic, a specific interrogation should be proposed more regularly in these patients in order to detect and to deal with, if possible, sexual disability.

L22 ANSWER 5 OF 9 EMBASE
on STN

ACCESSION NUMBER: 2003006586 EMBASE
TITLE: How natural are 'natural herbal remedies'? A Saudi perspective.
AUTHOR: Bogusz M.J.; Al Tufail M.; Hassan H.
CORPORATE SOURCE: Dr. M.J. Bogusz, Dept. of Pathology and Lab. Medecine, King Faisal Special. Hosp./Res. Ctr., PO Box 3354, Riyadh 11211, Saudi Arabia. mbogusz@web.de
SOURCE: Adverse Drug Reactions and Toxicological Reviews, (2002) 21/4 (219-229).
Refs: 30
ISSN: 0964-198X CODEN: ADRRER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: There is a rapidly growing trend in the consumption of herbal remedies in industrialised and developing countries. Users of herbal remedies are at risk of toxicity and adverse interactions of herbal preparations due to their frequent contamination with metals and adulteration with synthetic drugs. The purpose of this study was to assess the quality of herbal remedies present on the market in Saudi Arabia in recent years. Methodology: 247 herbal remedies and related preparations were examined from 2000-2001 at the Toxicology Laboratory, King Faisal **Specialist** Hospital and Research Centre, Riyadh, Saudi Arabia. Herbal powder samples were the most common sample type examined (n = 80), followed by complete, packed preparations (n = 59), single undescribed **capsules** or pills (n = 46), loose plant leaves or seeds (n = 28), creams (n = 18) and liquid or jelly samples (n = 16). All samples were subjected to toxicological screening for organic substances using gas chromatographic-mass spectrometric analysis, screening for heavy metals (arsenic, mercury, and lead) using inductive coupled plasma-mass spectrometry and microbiological examination. Results: The preparations analysed were used to treat the following indications: leukaemia and other forms of cancer (n = 22); obesity (n = 18); diabetes mellitus (n = 14); rheumatic disorders (n = 14); skin pigmentation problems (n = 11); or to enhance male sexual activity (n = 9). In 123 cases, the indication of use was not known. 39 samples contained high concentrations of heavy metals. This was particularly striking in remedies used to treat leukaemia (arsenic content of 522-161 600 ppm) and in creams for whitening skin (mercury content of 5 700-126 000 ppm). Eight preparations contained synthetic drugs (e.g. benzodiazepines and tricyclic antidepressants in sedative preparations, cyproheptadine in a remedy to gain bodyweight, ibuprofen and dipyrone in herbal **capsules** used to treat rheumatism). 18 samples were contaminated with micro-organisms. 14 samples contained toxic substances of natural origin. Of the 247 examined preparations, 77 (i.e. over 30%) were disqualified due to high heavy

metals content, bacterial contamination or presence of toxic organic substances. Conclusion: The study shows an urgent need to control the production, importing and selling of herbal preparations.

L22 ANSWER 6 OF 9 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-182862 [18] WPIDS
CROSS REFERENCE: 2001-182861 [14]
DOC. NO. CPI: C2001-054569
TITLE: **Capsule** formulations containing a **beta -carboline** phosphodiesterase inhibitor, exhibit good stability and bioavailability and are useful in treating **sexual dysfunction.**
DERWENT CLASS: A96 B02
INVENTOR(S): ANDERSON, N R; GULLAPALLI, R P
PATENT ASSIGNEE(S): (LILL-N) LILLY ICOS LLC
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001008687	A1	20010208	(200118)*	EN	31

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE 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 NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000044912	A	20010219	(200129)	
EP 1200091	A1	20020502	(200236)	EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001008687	A1	WO 2000-US11136	20000426
AU 2000044912	A	AU 2000-44912	20000426
EP 1200091	A1	EP 2000-926371	20000426
		WO 2000-US11136	20000426

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000044912	A	Based on	WO 2001008687
EP 1200091	A1	Based on	WO 2001008687

PRIORITY APPLN. INFO: US 1999-146924P 19990803
AN 2001-182862 [18] WPIDS
CR 2001-182861 [14]
AB WO 200108687 A UPAB: 20020610
NOVELTY - Soft **capsule** formulation containing (6R-trans)-6-(1,3-benzodioxol- 5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino- (1',2':1,6)pyrido(3,4-b)indole-1,4-dione (I) and a carrier is new.
DETAILED DESCRIPTION - Soft **capsule** comprises (a) a shell comprising gelatin which **encapsulates** (b) a pharmaceutical formulation comprising (i) the active agent (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-me thylpyrazino- (1',2':1,6)pyrido(3,4-

b)indole-1,4-dione (I) and (ii) a carrier.
ACTIVITY - Vasotropic.
MECHANISM OF ACTION - Cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase inhibitor.
USE - (I) is an inhibitor of type 5 cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase and is useful in treatment of **sexual dysfunction** e.g. male erectile dysfunction or female arousal disorder. (I) is disclosed in US5859006.
ADVANTAGE - The composition provides dosage uniformity and has good stability and bioavailability characteristics.
Dwg.0/0

L22 ANSWER 7 OF 9 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-182861 [18] WPIDS
CROSS REFERENCE: 2001-182862 [18]
DOC. NO. CPI: C2001-054568
TITLE: Formulations containing a **beta-carboline** compound useful as a phosphodiesterase inhibitor, exhibit good stability and bioavailability and are useful in treating **sexual dysfunction**.
DERWENT CLASS: A96 B02
INVENTOR(S): ANDERSON, N R; KRAL, M A; OREN, P L
PATENT ASSIGNEE(S): (LILL-N) LILLY ICOS LLC
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001008686	A1	20010208	(200118)*	EN	38
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE 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 NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000044909	A	20010219	(200129)		
BR 2000012863	A	20020416	(200234)		
NO 2002000532	A	20020326	(200235)		
EP 1200090	A1	20020502	(200236)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
SK 2002000173	A3	20020509	(200239)		
KR 2002014843	A	20020225	(200258)		
CZ 2002000386	A3	20020717	(200260)		
HU 2002002513	A2	20021028	(200277)		
CN 1365282	A	20020821	(200281)		
JP 2003505509	W	20030212	(200321)		29
ZA 2002000823	A	20030430	(200334)		46
NZ 516616	A	20030725	(200357)		
MX 2002001196	A1	20030201	(200413)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001008686	A1	WO 2000-US11130	20000426
AU 2000044909	A	AU 2000-44909	20000426
BR 2000012863	A	BR 2000-12863	20000426
		WO 2000-US11130	20000426

NO 2002000532	A	WO 2000-US11130	20000426
		NO 2002-532	20020201
EP 1200090	A1	EP 2000-926368	20000426
		WO 2000-US11130	20000426
SK 2002000173	A3	WO 1999-HU50	19990705
		SK 2002-173	20000705
KR 2002014843	A	KR 2002-701406	20020201
CZ 2002000386	A3	WO 2000-US11130	20000426
		CZ 2002-386	20000426
HU 2002002513	A2	WO 2000-US11130	20000426
		HU 2002-2513	20000426
CN 1365282	A	CN 2000-811036	20000426
JP 2003505509	W	WO 2000-US11130	20000426
		JP 2001-513416	20000426
ZA 2002000823	A	ZA 2002-823	20020130
NZ 516616	A	NZ 2000-516616	20000426
		WO 2000-US11130	20000426
MX 2002001196	A1	WO 2000-US11130	20000426
		MX 2002-1196	20020201

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000044909	A	Based on	WO 2001008686
BR 2000012863	A	Based on	WO 2001008686
EP 1200090	A1	Based on	WO 2001008686
SK 2002000173	A3	Based on	WO 2001008686
CZ 2002000386	A3	Based on	WO 2001008686
HU 2002002513	A2	Based on	WO 2001008686
JP 2003505509	W	Based on	WO 2001008686
NZ 516616	A	Based on	WO 2001008686
MX 2002001196	A1	Based on	WO 2001008686

PRIORITY APPLN. INFO: US 1999-146924P 19990803
AN 2001-182861 [18] WPIDS
CR 2001-182862 [18]
AB WO 200108686 A UPAB: 20040223
NOVELTY - The phosphodiesterase inhibitor (6R-trans)-6-(1,3-benzodioxol-5-yl)- 2,3,6,7,12,12a-hexahydro-2-methylpyrazino- (1',2':1,6)pyrido(3,4-b)indole-1,4-dione(I) is formulated with a water-soluble diluent, a lubricant, a hydrophilic binder and a disintegrant to improve its dosage uniformity and stability and bioavailability properties.

DETAILED DESCRIPTION - Pharmaceutical formulation comprises: (a) the compound (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino- (1',2':1,6)pyrido(3,4-b)indole-1,4-dione (I), as the free drug; (b) a water-soluble diluent; (c) a lubricant; (d) a hydrophilic binder which is a cellulose derivative and/or povidone; and (e) a disintegrant which is croscarmellose sodium and/or crospovidone.

ACTIVITY - Vasotropic.

MECHANISM OF ACTION - Cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase inhibitor.

USE - (I) is an inhibitor of type 5 cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase and is useful in treatment of **sexual dysfunction** e.g. male erectile dysfunction or female arousal disorder. (I) is disclosed in US5859006.

ADVANTAGE - The formulation provides dosage uniformity and has good stability and bioavailability characteristics.

Dwg.0/0

L22 ANSWER 8 OF 9 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1997-087305 [08] WPIDS
DOC. NO. CPI: C1997-028406
TITLE: New tetra hydro-**beta-carboline** derivs. with benzo heterocyclic gp. - used to treat disorders associated with dysfunction of 5-HT-2C receptors e.g. CNS, sleep and eating disorders and **sexual dysfunction.**
DERWENT CLASS: B02
INVENTOR(S): HANSEN, J B; HANSEN, J
PATENT ASSIGNEE(S): (NOVO) NOVO-NORDISK AS
COUNTRY COUNT: 71
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9700871	A1	19970109	(199708)*	EN	25
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN					
AU 9662981	A	19970122	(199719)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9700871	A1	WO 1996-DK258	19960614
AU 9662981	A	AU 1996-62981	19960614

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9662981	A	Based on	WO 9700871

PRIORITY APPLN. INFO: DK 1995-722 19950623
AN 1997-087305 [08] WPIDS
AB WO 9700871 A UPAB: 19970220
Tetrahydro-**beta-carboline** derivs. of formula (I) and their salts are new. R1, R2 = H, 1-6C alkyl, 3-6C cycloalkyl, 1-6C alkoxy, aralkyl, halo, haloalkyl, NO2 or 1-6C alkylthio; R3, R5, R6 = H, 1-6C alkyl, 2-6C alkenyl or 3-6C cycloalkyl; R4 = a benzo-fused heterocyclic gp. of formula (a); A-B-Y = together with the 2C's of the benzene ring forms a 5 membered heterocyclic ring containing one or more N, O or S atoms, opt. substd. with one or more of H, halo, 1-6C alkyl, 2-6C alkenyl, NO2, haloalkyl or 3-6C cycloalkyl; R7, R8 = H, halo, 1-6C alkyl, 2-6C alkenyl, NO2, CN, haloalkyl or 3-6C cycloalkyl.

USE - (I) are used in the treatment of disorders of the central nervous system, sleep disorders, eating disorders or **sexual dysfunctions** which are influenced by dysfunction of the 5-HT2c receptors (claimed). (I) have high affinity for the 5HT2c receptor and can be used to treat psychiatric and neurological disorders; such as schizophrenia, anxiety, depression, obsessive-compulsive disorders, panic and diseases related to sleep, appetite, thermoregulation, sexual behaviour, motor activity and neuroendocrine function and to treat brain oedema.

Tablets contain 0.05-500mg pref. 1-100mg/**tablet**. Admin. may be oral, suppositories or parenteral.

Dwg.0/0

L22 ANSWER 9 OF 9 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1992-042839 [06] WPIDS
DOC. NO. CPI: C1992-018796
TITLE: Solid oral ifosfamide dosage forms - comprising **capsules** containing **microcrystalline cellulose**, or **tablets** containing tri calcium phosphate and polyethylene glycol, etc..
DERWENT CLASS: A96 B03 B07
INVENTOR(S): ENGEL, J; MILSMANN, E; SAUERBIER, D; ISAAC, O; MOLGE, K; HORST, R
PATENT ASSIGNEE(S): (ASTA) ASTA PHARMA AG; (SAUE-I) SAUERBIER D; (ASTA) ASTA MEDICA AG
COUNTRY COUNT: 32
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 469440	A	19920205	(199206)*		
R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
DE 4124481	A	19920206	(199207)		
NO 9103019	A	19920204	(199215)		
AU 9181589	A	19920206	(199216)		
CA 2048367	A	19920204	(199217)		
FI 9103710	A	19920204	(199219)		
ZA 9106124	A	19920429	(199223)		15
HU 59316	T	19920528	(199227)		
PT 98532	A	19920630	(199230)		
CS 9102409	A2	19920318	(199241)		
CN 1058715	A	19920219	(199242)		
JP 04243828	A	19920831	(199242)		6
US 5158776	A	19921027	(199246)		5
NZ 239222	A	19930127	(199310)		
AU 643309	B	19931111	(199401)		
AU 9344836	A	19931111	(199401)		
AU 649184	B	19940512	(199425)		
EP 469440	B1	19940824	(199433)	GE	7
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE					
DE 59102620	G	19940929	(199438)		
ES 2058999	T3	19941101	(199444)		
NO 178252	B	19951113	(199550)		
IE 66378	B	19951227	(199609)		
CZ 280475	B6	19960117	(199610)		
IL 99031	A	19960804	(199646)		
FI 97951	B	19961213	(199704)		
RO 113611	B1	19980930	(199851)		
SK 279739	B6	19990312	(199919)		
SK 279740	B6	19990312	(199919)		
JP 3061898	B2	20000710	(200037)		6
CA 2048367	C	20000523	(200039)	EN	
KR 177170	B1	19990320	(200043)		
JP 2000229860	A	20000822	(200045)		6

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 469440	A	EP 1991-112368	19910724
DE 4124481	A	DE 1991-4124481	19910724

FI 9103710	A		FI 1991-3710	19910802
ZA 9106124	A		ZA 1991-6124	19910802
HU 59316	T		HU 1991-2594	19910802
PT 98532	A		PT 1991-98532	19910801
CS 9102409	A2		CS 1991-2409	19910802
CN 1058715	A		CN 1991-105271	19910802
JP 04243828	A		JP 1991-191414	19910731
US 5158776	A		US 1991-733756	19910724
NZ 239222	A		NZ 1991-239222	19910801
AU 643309	B		AU 1991-81589	19910802
AU 9344836	A	Div ex	AU 1991-81589	19910802
			AU 1993-44836	19930823
AU 649184	B	Div ex	AU 1991-81589	19910802
			AU 1993-44836	19930823
EP 469440	B1		EP 1991-112368	19910724
DE 59102620	G		DE 1991-502620	19910724
			EP 1991-112368	19910724
ES 2058999	T3		EP 1991-112368	19910724
NO 178252	B		NO 1991-3019	19910802
IE 66378	B		IE 1991-2774	19910802
CZ 280475	B6		CS 1991-2409	19910802
IL 99031	A		IL 1991-99031	19910801
FI 97951	B		FI 1991-3710	19910802
RO 113611	B1		RO 1991-148008	19910715
SK 279739	B6		SK 1998-543	19910802
SK 279740	B6		CS 1991-2409	19910802
JP 3061898	B2		JP 1991-191414	19910731
CA 2048367	C		CA 1991-2048367	19910802
KR 177170	B1		KR 1991-13365	19910802
JP 2000229860	A	Div ex	JP 1991-191414	19910731
			JP 2000-6836	19910731

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 643309	B	Previous Publ.	AU 9181589
AU 649184	B	Previous Publ.	AU 9344836
DE 59102620	G	Based on	EP 469440
ES 2058999	T3	Based on	EP 469440
NO 178252	B	Previous Publ.	NO 9103019
CZ 280475	B6	Previous Publ.	CS 9102409
FI 97951	B	Previous Publ.	FI 9103710
SK 279739	B6	Previous Publ.	CS 9800543
SK 279740	B6	Previous Publ.	CS 9102409
JP 3061898	B2	Previous Publ.	JP 04243828

PRIORITY APPLN. INFO: DE 1990-4024683 19900803
AN 1992-042839 [06] WPIDS
AB EP 469440 A UPAB: 19931122
Oral ifosfamide (I) dosage forms comprise: (A) **capsules** containing a compsn. comprising (I), **microcrystalline cellulose** (MC) and opt. small amts. of conventional flow improvers and mould release agents; or (B) **tablets** comprising 1 pt. weight (I), 0.1-1 pt. weight tricalcium phosphate and 0.04-0.4 pt. weight polyethylene glycol, where the **tablets** also contain 5-60 weight% flow improver, 1-10% disintegrant, 0.1-10% mould release agent and 0.1-80% binder. (I) is 3-(2-chloroethyl)-2-(chloroethylamino) -tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide.
USE/ADVANTAGE - (I) is a cytostatic agent. The dosage forms have good

storage stability, overcoming problems associated with the hygroscopicity of (I). @(8pp Dwg.No.0/0
0/0

ABEQ US 5158776 A UPAB: 19931006
Solid oral ifosfamide (I) formulation comprises ifosfamide **capsules** (IC) having a **capsule** mass consisting of (I) ad **microcrystalline cellulose** having a deg. of crystallinity of 0.5-0.9 or ifosfamide **tablets** (IT) comprising: 0.1-1 wt. pts. tribasic Ca phosphate, 0.04-0.4 wt. pts. polyethylene glycol; 5-60 wt. % filing and flow regulating agent; 1-10 wt. % disintegrant; 0.1-10 wt. % antiadhesion agent; and 0.1-80 wt. % binding agent.

Pref. the IC contains conventional flow regulating and antiadhesion agents.

USE/ADVANTAGE - (I) is a cytostatically active medication. There is no deleterious interaction between (I) and the **capsule** wall allowing oral admin. overcoming the unpleasant painful parenteral therapy which can only be performed by **specialised** medical personnel.
0/0

ABEQ EP 469440 B UPAB: 19941010
A solid oral ifosfamide formulation, characterised in that it takes the form of ifosfamide **capsules**, the weight of the **capsule** consisting essentially of the active ingredient, ifosfamide, and **microcrystalline cellulose**, optionally with additional smaller amounts of a conventional flow regulator and antiadhesion agent, or in that it takes form of **tablets** containing, based on one part by weight of ifosfamide, 0.1 - 1.0 part by weight of tricalcium phosphate and 0.04 - 0.4 part by weight of polyethylene glycol, and additionally containing, based on the weight of the **tablet**, 5 - 60% by weight of a filler, and flow regulator, 1 - 10% by weight of a disintegrating agent, 0.1 - 10% by weight of an antiadhesion agent and 0.1 - 80% by weight of a binder.
Dwg.0/0

Inventor Search

=> d ibib abs hitstr ind l8 1-3

L8 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:100983 HCAPLUS
DOCUMENT NUMBER: 134:152655
TITLE: Pharmaceutical compositions containing β-**carboline** drugs
INVENTOR(S): **Anderson, Neil R.**; Hartauer, Kerry J.; **Kral, Martha A.**; Stephenson, Gregory A.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008688	A2	20010208	WO 2000-US20981	20000801
WO 2001008688	A3	20010816		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000012901	A	20020416	BR 2000-12901	20000801
EP 1200092	A2	20020502	EP 2000-952371	20000801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505510	T2	20030212	JP 2001-513418	20000801
NZ 516613	A	20030829	NZ 2000-516613	20000801
ZA 2002000825	A	20030207	ZA 2002-825	20020130
NO 2002000531	A	20020403	NO 2002-531	20020201

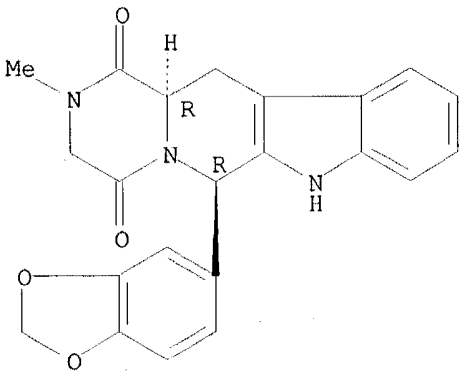
PRIORITY APPLN. INFO.: US 1999-147048P P 19990803
WO 2000-US20981 W 20000801

AB Pharmaceutical compns. containing β- **carboline** drugs and pharmaceutically acceptable salts and solvates thereof, wherein the drug is in free particulate form, is disclosed. A tablet contained a β-**carboline** drug 10.00, lactose monohydrate 153.80, spray dried lactose monohydrate 25.00, hydroxypropyl cellulose 4.00, croscarmellose sodium 16.00, hydroxypropyl cellulose 1.75, sodium lauryl sulfate 0.70, microcryst. cellulose 37.50, and magnesium stearate 1.25 mg. The improvement in bioavailability of the drug was demonstrated in humans.

IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing β- **carboline** drugs)

RN 171596-29-5 HCAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IC ICM A61K031-4985
ICS A61K009-14; A61P015-10
CC 63-6 (Pharmaceuticals)
ST pharmaceutical tablet beta **carboline** drug bioavailability
IT Sexual behavior
(disorder; pharmaceutical compns. containing β- **carboline** drugs)
IT Sexual behavior
(impotence; pharmaceutical compns. containing β- **carboline** drugs)
IT Dissolution rate
Drug bioavailability
Particle size
(pharmaceutical compns. containing β- **carboline** drugs)
IT Drug delivery systems
(tablets; pharmaceutical compns. containing β- **carboline** drugs)
IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing β- **carboline** drugs)

L8 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:100982 HCAPLUS
DOCUMENT NUMBER: 134:152654
TITLE: β- **Carboline** pharmaceutical compositions
INVENTOR(S): **Anderson, Neil R.**; Gullapalli, Rampurna P.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008687	A1	20010208	WO 2000-US11136	20000426

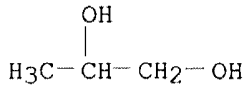
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1200091 A1 20020502 EP 2000-926371 20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
ZA 2002000823 A 20030204 ZA 2002-823 20020130
PRIORITY APPLN. INFO.: US 1999-146924P P 19990803
WO 2000-US11136 W 20000426

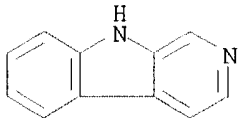
AB β- **Carboline** soft capsules contains a solution or suspension of a PDE5 inhibitor, and are useful for treating sexual dysfunction. Thus, a formulation contained a β- **carboline** 25.0, Capmul MCM 177.5, Gelucire 44/14 177.5, and propylene glycol 20.0 mg/capsule. In the phys. study of the above capsule formulation, no sedimentation was observed after storage at 4° for 120 days.

IT **57-55-6**, Propylene glycol, biological studies **244-63-3D**, β- **Carboline**, analogs **9003-39-8**, PVP **25322-68-3**, Polyethylene glycol **31692-85-0**, Glycofurol **121548-04-7**, Gelucire 44/14 **156259-68-6**, Capmul MCM **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β- **carboline** pharmaceutical compns.)

RN 57-55-6 HCAPLUS
CN 1,2-Propanediol (8CI, 9CI) (CA INDEX NAME)



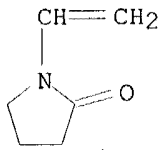
RN 244-63-3 HCAPLUS
CN 9H-Pyrido[3,4-b]indole (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



RN 25322-68-3 HCAPLUS
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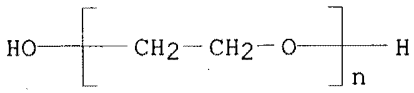
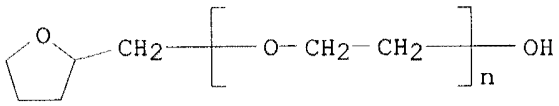


RN 31692-85-0 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-[(tetrahydro-2-furanyl)methyl]-ω-hydroxy- (9CI) (CA INDEX NAME)

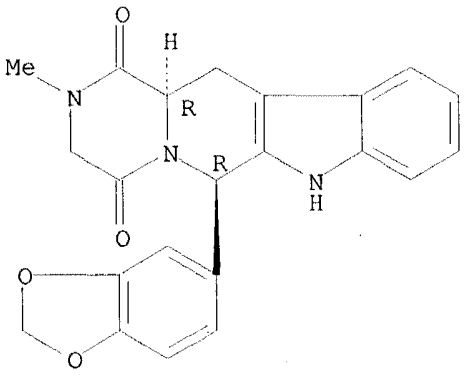


RN 121548-04-7 HCAPLUS
CN Gelucire 44/14 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 156259-68-6 HCAPLUS
CN Capmul MCM (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 171596-29-5 HCAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IC ICM A61K031-495
ICS A61P015-10; A61K009-48
CC 63-6 (Pharmaceuticals)
ST **carboline** capsule glyceride PEG
IT Monoglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10; β- **carboline** pharmaceutical compns.)
IT Drug delivery systems
(capsules; β- **carboline** pharmaceutical compns.)
IT Sexual behavior
(disorder; β- **carboline** pharmaceutical compns.)
IT Gelatins, biological studies
Polyoxyalkylenes, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β- **carboline** pharmaceutical compns.)

IT **57-55-6**, Propylene glycol, biological studies **244-63-3D**, β- **Carboline**, analogs **9003-39-8**, PVP **25322-68-3**, Polyethylene glycol **31692-85-0**, Glycofurol **121548-04-7**, Gelucire 44/14 **156259-68-6**, Capmul MCM **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β- **carboline** pharmaceutical compns.)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:100981 HCAPLUS
DOCUMENT NUMBER: 134:152653
TITLE: β- **Carboline** pharmaceutical compositions containing cellulose
INVENTOR(S): Oren, Peter L.; **Anderson, Neil R.**; **Kral, Martha A.**
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008686	A1	20010208	WO 2000-US11130	20000426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000012863	A	20020416	BR 2000-12863	20000426
EP 1200090	A1	20020502	EP 2000-926368	20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505509	T2	20030212	JP 2001-513416	20000426
NZ 516616	A	20030725	NZ 2000-516616	20000426
ZA 2002000823	A	20030204	ZA 2002-823	20020130
NO 2002000532	A	20020326	NO 2002-532	20020201

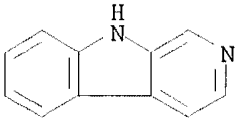
PRIORITY APPLN. INFO.: US 1999-146924P P 19990803
WO 2000-US11130 W 20000426

AB β- **Carboline** formulations contain a c-GMP phosphodiesterase inhibitor, a water-soluble diluent, a lubricant, a hydrophilic binder, a disintegrant, and optional microcryst. cellulose and/or a wetting agent, are useful for treating sexual dysfunction. Thus, a tablet formulation contained a β- **carboline** 5.00, lactose monohydrate 109.655, lactose monohydrate (spray dried) 17.50, Hydroxypropyl cellulose 4.025, croscarmellose sodium 6.30, SLS 0.49, microcryst. cellulose (granular-102) 26.25, croscarmellose sodium 4.90, and Mg stearate 0.88 mg/tablet.

IT **244-63-3D**, β- **Carboline**, analogs **9003-39-8**, Povidone **25322-68-3**, Polyethylene glycol **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(β- **carboline** pharmaceutical compns. containing cellulose)

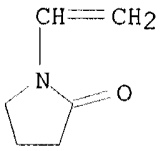
RN 244-63-3 HCAPLUS
CN 9H-Pyrido[3,4-b]indole (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



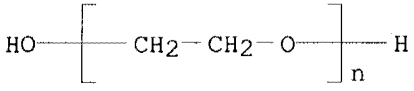
RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O

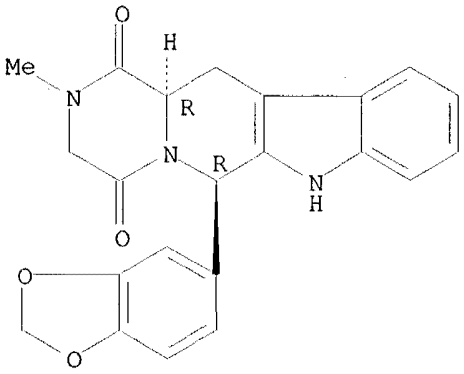


RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



RN 171596-29-5 HCAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



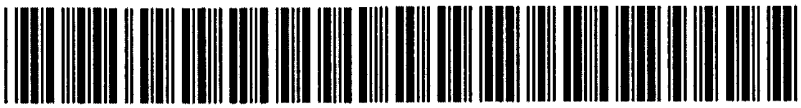
IC ICM A61K031-495

ICS A61K009-20; A61P015-10
CC 63-6 (Pharmaceuticals)
ST beat **carboline** pharmaceutical cellulose
IT Monoglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetates; β- **carboline** pharmaceutical compns. containing cellulose)
IT Sexual behavior
(disorder; β- **carboline** pharmaceutical compns. containing cellulose)
IT Castor oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated; β- **carboline** pharmaceutical compns. containing cellulose)
IT Alcohols, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydric; β- **carboline** pharmaceutical compns. containing cellulose)
IT Drug delivery systems
(tablets; β- **carboline** pharmaceutical compns. containing cellulose)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vegetable, hydrogenated; β- **carboline** pharmaceutical compns. containing cellulose)
IT Particle size distribution
Wetting agents
(β- **carboline** pharmaceutical compns. containing cellulose)
IT Diglycerides
Hydrocarbon oils
Polyoxyalkylenes, biological studies
Polysaccharides, biological studies
Waxes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β- **carboline** pharmaceutical compns. containing cellulose)
IT 7631-86-9, Silica, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(colloidal; β- **carboline** pharmaceutical compns. containing cellulose)
IT 9068-52-4, CGMP Phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; β- **carboline** pharmaceutical compns. containing cellulose)
IT 50-70-4, Sorbitol, biological studies 50-99-7, Dextrose, biological studies 57-11-4, Stearic acid, biological studies 57-50-1, Sucrose, biological studies 63-42-3, Lactose 69-65-8, Mannitol 87-99-0, Xylitol 151-21-3, SLS, biological studies **244-63-3D**, β-**Carboline**, analogs 532-32-1, Sodium benzoate 557-04-0 577-11-7, Sodium docusate 1344-95-2, Calcium silicate 1592-23-0 4070-80-8, Sodium stearyl fumarate **9003-39-8**, Povidone 9004-34-6D, Cellulose, derivs., biological studies 9004-64-2, Hydroxypropyl cellulose 9004-65-3, HPMC 9005-25-8, Starch, biological studies 9005-65-6, Polysorbate 80 9050-36-6, Maltodextrin 12619-70-4, Cyclodextrin 14807-96-6, Talc, biological studies 18641-57-1, Glyceryl behenate **25322-68-3**, Polyethylene glycol 64044-51-5, Lactose monohydrate 74811-65-7, Croscarmellose sodium 106392-12-5, Poloxamer **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β- **carboline** pharmaceutical compns. containing cellulose)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

US 099604710DP1



Creation date: 06-02-2004
Indexing Officer: FQUIZON - FLORINDA QUIZON
Team: OIPEScanning
Dossier: 09960471

Legal Date: 06-02-2004

No.	Doccode	Number of pages
1	ABN	2
2	EXIN	2

Total number of pages: 4

Remarks:

Order of re-scan issued on .....

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

4743 7590 06/02/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S Channavajjala	1615	

-- 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) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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) *1-26* 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) *1-26* 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-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-24-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of IDS dated 6-24-02 is acknowledged.

Claim 27 has been canceled and claims 1-26 are pending in the instant application.

Claims 1is directed to a pharmaceutical composition comprising a beta-carboline (formula I) as a free drug, a diluent, a lubricant, disintegrant and a binder. Claims 2-16 & 19 dependent from claim 1 recite the specific excipients and percentages of the excipients. Dependent claim 17 recites that drug is provided as particles and 90% of the particles have a size less than 40 microns. Claim 18 recites particle size as less than 10 microns. Claims 20-21 depend from claim 18. Claims 22-24 recite a tablet comprising composition of claim 1 and, claim 25 recites a capsule comprising composition of claim 1. Claim 26 is directed to a method of treating a patient in need thereof with the composition of any one of claims 1-21.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7, 9, 11-16 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/03675 (Daugan).

Daugan discloses the claimed beta-carboline compounds and compositions containing the compounds, as also acknowledged by applicants on page 2 of the instant application. Daugan specifically discloses instant preferred compound (instant specification, page 3, lines 28-30) for treating conditions where inhibition of PDE5 is beneficial (see page 3, lines 24-25, lines 30-32 and is also referred to as compound A). On page 12, lines 11-12, Daugan discloses that the compounds a and B are prepared as different dosage forms and in particular, Table B shows a tablet prepared by wet granulation, where in the tablet composition contains beta-carboline drug as active agent and other excipients such as polyvinylpyrrolidone, PEG, Polysorbate 80, magnesium stearate, crosscaramellose sodium, and microcrystalline cellulose, which read on the instant claimed binder, diluent, wetting agent, lubricant and disintegrant respectively. Instant dependent claims specifically recite the excipients of Table B of Daugan. With respect to the percentages of active ingredients and the excipients claimed, the total weight of the composition of tablet in Table B is 500 mg. A calculation of the proportion of each ingredient in Table 2 reads on the instant claimed percentages. With respect to the claimed "free drug", Daugan does not teach an intimately embedded drug in a polymeric co-precipitate and hence meets the definition of instant "free drug" (instant page 5, lines 24-27). Instead, Daugan only discloses direct compression or wet granulation followed by compression to prepare the tablets (pages 12-14). Accordingly, Daugan anticipates instant claims.

Claim Rejections - 35 USC § 103

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.

Claims 5, 8, 10, 19 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03675 (Daugan).

Daugan, discussed above, fails to teach the exact or the percentages of diluent (claim 5), lubricant (claim 8), binder (claim 10), and the claimed amounts of drug in tablet (claims 22, 23) and capsule (claim 25). However as acknowledged by applicants, Daugan teaches the active agent and also for the same purposes i.e., as a 5PDE inhibitor. Further Daugan teaches the same pharmaceutical compositions containing the same active compound and excipients, as claimed, in the form of tablets and capsules. Accordingly, optimizing the amounts of art recognized excipients such as binder, lubricant, optimizing the amount of active compound with an expectation to achieve the appropriate dosage form as well the desired therapeutic efficiency of the drug would have been within the scope of a skilled artisan because Daung suggests optimizing the amounts of drug in the range of 0.5 to 800 mg per day and also employing the suitable excipients depending on the route of administration (page 5).

Claims 17, 18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03675 (Daung) as applied to claims 1-16, 19, 22-26 above, and further in view of WO 96/38131 (Butler) and US 4,721,709 to Seth et al (Seth).

Instant claims recite particulate drug and in particular, where at least 90% of the particles have a size of less than 40 microns (claim 17) or less than 10 microns (claim 18). Daung fails to teach drug particles, as claimed.

Butler teaches pharmaceutical compositions comprising beta-carboline compounds (abstract, page 4, lines 15-21). The specific beta-carboline compound taught by Butler is the same as that claimed in the instant invention. Further, Butler teaches that the above are poorly soluble in nature. Butler teaches solid dispersions but fails to teach the claimed particle sizes.

Seth teaches pharmaceutical composition containing poorly water-soluble drugs and a method of preparing the same. The method of Seth is practically applicable to all water insoluble drugs and comprises the steps of providing dry powder of the insoluble drug that is adsorbed on to a carrier such as starch or cellulose and is characterized in that the drug is present particulate form and at least 95% of the drug particles have a mean size of less than 15 microns (col. 4, lines 44-53, col. 3, lines 60-67), which is in the same range as claimed. Seth teaches that the drug particles are closely associated with the carrier and details the method of preparing the formulation in col. 6, lines 1-39. Further, Seth teaches preparation of various dosage forms such as tablets, capsules etc., with the above prepared formulation (col. 8). Examiner notes that instant specification refers to US patent 4,605,517 by incorporation for the preparation of the instant drug formulation. It is noted that the above patent also recites the same method of preparation as that of Seth. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare drug formulations of beta-carboline of Daugan containing the excipients such as lubricants, wetting agents etc., by the process of Seth i.e., particulate drug adsorbed on to excipients or carrier and compressing into tablets because Seth teaches that the

conventional methods of jet milling or pin milling employed in drug preparation result in slow dissolution and absorption, (col. 2, lines 1-20) and that their method avoids the disadvantages of agglomeration and poor flow seen in the conventional methods. Accordingly, the expected result would be an increased dissolution of beta-carboline and hence increased bioavailability without agglomeration.

Double Patenting

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. See *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) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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).

Claims 1-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 8, 9, 12-21 and 22-24 of copending Application No. 10/031,531and over claims 1-9 and14-16 of copending Application No. 10/031,463. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claimed composition containing a free drug, beta-carboline together with excipients and also composition comprising particulate form of the drug is also claimed in the above patent applications. US application 10/031,531 the composition

of the instant claims in the form of capsules, which is reads on the claimed subject matter of instant claim 25. Further, method of treating specific disorders using the above composition by '131 anticipates instant method of treatment. Accordingly, claims of application 10/031,531 anticipate instant claims.

US application 10/031,463 claims a free drug particulate form of beta-carboline, compositions containing the free drug, a method of treating a patient in need thereof. The copending claims also recite particle sizes, carriers or excipients, which read on the instant dependent claims. Accordingly, the copending claims directed specifically to particulate beta-carboline compound, composition containing particulate compound anticipate instant broadly recited pharmaceutical compositions and method claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-26 are directed to an invention not patentably distinct from claims 1, 4, 8, 9, 12-21 and 22-24 of commonly assigned 10/031,531. Specifically, the copending application describes pharmaceutical compositions containing the same drug, i.e., beta-carboline compounds, in the form of free drug and also in particulate form and for the treatment of the same disease or disorders, also described in the instant application.

Claims 1-26 are directed to an invention not patentably distinct from claims 1-9 and14-16 of commonly assigned Application No. 10/031,463. Specifically, the copending application describes pharmaceutical compositions containing the same drug, i.e., beta-carboline

compounds, in the form of free drug and also in particulate form and for the treatment of the same disease or disorders, also described in the instant application.

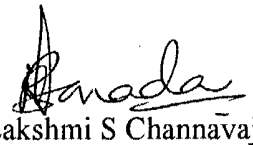
The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 10/031,151 and 10/031,463, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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).



Lakshmi S Channavajjala
Examiner
Art Unit 1615
May 29, 2004

Form 1449PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/031,464
Filing Date	April 29, 2002
First Named Inventor	Peter L. Oren et al.
Group Art Unit	1614
Examiner Name	Unassigned
Attorney Docket Number	29342/36230A

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY
		WO 96/38131 (PCT)	12/05/96
		WO 98/23270 (PCT)	06/04/98
		WO 97/03675 (PCT)	02/06/97

OTHER PRIOR ART – NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	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.

Examiner Signature	L. Channavajjala	Date Considered	5/28/04

*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.

Notice of References Cited	Application/Control No. 10/031,464	Applicant(s)/Patent Under Reexamination OREN ET AL.	
	Examiner Lakshmi S Channavajjala	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-4,721,709	01-1988	Seth et al.	514/221
	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					
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	P					
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	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	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.

Search Notes

Application No.	Applicant(s)	
10/031,464	OREN ET AL.	
Examiner	**Art Unit**	
Lakshmi S Channavajjala	1615	

SEARCHED			
Class	Subclass	Date	Examiner
424	464		
	451		
	489		
514	182		
	258	5/28/2004	LC

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
WEST-USPAT, PGPUB, DWPI, EPAB, JPAB-INCLUDING INVENTOR NAME	5/28/2004	LC
LIBRARY- STN SEACRCH - ATTACHED	5/28/2004	LC
PALM INVENTOR NAME SEARCH	5/28/2004	LC

Index of Claims

Application No.	Applicant(s)	
10/031,464	OREN ET AL.	
Examiner	**Art Unit**	
Lakshmi S Channavajjala	1615	

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PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: **September 24, 2004**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

AMENDMENT "A"

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

Sir:

In response to the Office Action of June 2, 2004, please amend the above-identified application as follows. Reconsideration and allowance of the application are respectfully requested.

09/28/2004 EAREGAY1 00000036 10031464

01 FC:1202 1116.00 OP
02 FC:1203 290.00 OP

IN THE SPECIFICATION:

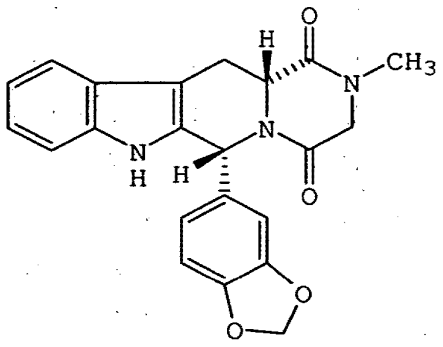
Please insert the abstract provided on a separate sheet accompanying this amendment.

Please amend the paragraph at page 10, lines 6-15 to read as follows:

--A preferred hydrophilic binder is a cellulose derivatives, including, for example, hydroxypropylcellulose and hydroxypropyl methylcellulose. Another nonlimiting hydrophilic binder is povidone. Preferably, the amount of hydrophilic binder present in the formulation is about 1% to about 5%, by weight of the formulation.--

IN THE CLAIMS:

1. (Currently amended) A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles have a particle size of less than about 40 microns; a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

2. (Original) The formulation of claim 1 further comprising microcrystalline cellulose.

3. (Original) The formulation of claim 1 further comprising a wetting agent.

4. (Original) The formulation of claim 1 wherein the active compound is present in an amount of about 0.5% to about 10% by weight.

5. (Original) The formulation of claim 1 wherein the water-soluble diluent is present in an amount of about 50% to about 85% by weight.

6. (Original) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of a sugar, a polysaccharide, a polyol, a cyclodextrin, and mixtures thereof.

7. (Currently amended) The formulation of claim ~~3~~ 1 wherein the water-soluble diluent is selected from the group consisting of lactose, sucrose, dextrose, a dextrate, a maltodextrin, mannitol, xylitol, sorbitol, a cyclodextrin, and mixtures thereof.

8. (Original) The formulation of claim 1 wherein the lubricant is present in an amount of about 0.25% to about 2% by weight.

9. (Original) The formulation of claim 1 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, hydrogenated vegetable oils, and mixtures thereof.

10. (Original) The formulation of claim 1 wherein the hydrophilic binder is present in an amount of about 1% to about 5% by weight.

11. (Original) The formulation of claim 1 wherein the cellulose derivative is selected from the group consisting of hydroxypropylcellulose, hydroxypropyl methylcellulose, and mixtures thereof.

12. (Original) The formulation of claim 1 wherein the disintegrant is present in an amount of about 3% to about 10% by weight.

13. (Original) The formulation of claim 2 wherein the microcrystalline cellulose is present in an amount of about 5% to about 40% by weight.

14. (Original) The formulation of claim 3 wherein the wetting agent is present in an amount of 0.1% to about 5% by weight.

15. (Original) The formulation of claim 14 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, docusate sodium, ethoxylated castor oil, a polyglycolyzed glyceride, an acetylated monoglyceride, a sorbitan fatty acid ester, a poloxamer, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene, a monoglyceride and ethoxylated derivatives thereof, a diglyceride and ethoxylated derivatives thereof, and mixtures thereof.

16. (Currently amended) The formulation of claim ~~1~~ 15 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, polysorbate 80, and a mixture thereof.

17. (Cancelled)

18. (Original) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 10 microns.

19. (Original) The formulation of claim 1 comprising:

(a) about 1% to about 4% by weight of the active compound;

(b) about 50% to about 75% by weight lactose;

(c) about 0.25% to about 2% by weight magnesium stearate;

(d) about 1% to about 5% by weight hydroxypropyl cellulose; and

(e) about 3% to about 10% by weight croscarmellose sodium.

20. (Original) The formulation of claim 18 further comprising about 5% to about 40% by weight microcrystalline cellulose.

21. (Original) The formulation of claim 18 further comprising about 0.1% to about 5% by weight sodium lauryl sulfate.

22. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 20 mg per tablet.

23. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 to about 15 mg per tablet.

24. (Currently amended) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 mg ~~or about 10 mg~~ per tablet.

25. (Original) A capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles, wherein the active compound is present in an amount of about 1 to about 20 mg per capsule.

26. (Cancelled)

27. (Cancelled)

28. (New) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 30 microns.

29. (New) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 25 microns.

30. (New) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 15 microns.

31. (New) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 10 mg per tablet.

32. (New) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 5 mg per tablet.

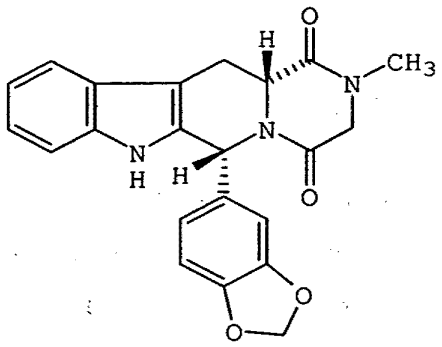
33. (New) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 2.5 mg per tablet.

34. (New) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 20 mg per tablet.

35. (New) A method of treating sexual dysfunction in a patient in need thereof comprising administering to the patient an effective amount of a formulation or a tablet according to of any one of claims 1 through 25 or claims 28 through 30.

36. (New) The method of claim 35 wherein the sexual dysfunction is male erectile dysfunction.

37. (New) A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles have a particle size of less than about 40 microns; a water-soluble diluent, a lubricant; a hydrophilic binder; and a disintegran.

REMARKS

Claims 1-26 are pending in the application. Claims 17 and 26 have been cancelled by this amendment. Claim 27 was cancelled previously. New claims 28-37 have been added to the application. Therefore, claims 1-16, 18-25, and 28-37 are at issue.

Claim 1 has been amended to incorporate the features of originally filed, and now-cancelled, claim 17. Claims 7 and 16 have been amended to correct the dependency of these claims. Claim 24 has been amended to delete the feature of 10 mg of active compound per tablet. This feature now is recited in new claim 31. Claim 24 serves as support for new claim 31.

New claims 28-30 recite additional particle sizes for the free drug. Support for new claims 28-30 can be found at page 8, lines 14-27 of the specification.

New claims 32-34 recite amounts of active compound present in a tablet. Support for new claims 32-34 can be found in Example 3 (containing 2.5 mg of active compound) and at page 13, lines 9-18 of the specification.

Cancelled claim 26 has been rewritten as new claim 35. New claim 36 recites that the sexual dysfunction is male erectile dysfunction. Support for new claim 36 can be found in the specification at page 4, lines 26-29. New claim 37 recites the particle size of the free drug as well as formulation ingredients. Support for claim 37 is found in claim 1 and claim 17 (cancelled herein).

The specification is objected to for failing to contain an abstract. In response, applicants submit

an abstract, on a separate sheet, concurrently with this amendment. The specification also has been amended at page 10 to delete "hydroxyethylcellulose" and "hydroxybutylmethylcellulose" as hydrophilic binders.

Claims 1-4, 6, 7, 9, 11-16, and 26 stand rejected under 35 U.S.C. §102(b) as being anticipated by WO 97/03675 (WO '675). Claims 5, 8, 10, 19, and 22-25 stand rejected under 35 U.S.C. §103 as being unpatentable over WO '675. For the reasons set forth below, it is submitted that all pending claims are patentable over WO '675.

In particular, claim 17 was not included in these rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103 based on WO '675. In view of the amendment to claim 1, which incorporates the features of claim 17, the rejections of the claims over WO '675 alone are moot and should be withdrawn.

Claims 17, 18, 20, and 21 stand rejected under 35 U.S.C. §103 as being unpatentable over WO '675 in view of WO 96/38131 (WO '131) and U.S. Patent No. 4,721,709 ('709). Claim 17 has been cancelled herein, and the features of claim 17 incorporated into claim 1. For the reasons set forth below, it is submitted that this rejection is in error and should be withdrawn.

The patentability of all pending claims over WO '675 has been discussed above. In addition, claim 1 recites a particle size for Compound (I), which the examiner explicitly states that WO '675 *fails* to teach (see page 5 of the Office Action).

Furthermore, the presently claimed formulations are a result of substantial research directed to

providing a stable composition that effectively delivers the claimed compound (i.e., Compound (I)) *in vivo*. Compound (I) is a highly water-insoluble drug and its formulation into a pharmaceutical composition that effectively delivers the drug is not straightforward. As a result of applicants' investigation, a pharmaceutical composition that is physically stable, and that demonstrates improved dissolution and *in vivo* absorption has been achieved.

In view of the above, the '675 patent has failed to teach or suggest the present invention as a whole. Accordingly, it is submitted that the pending claims would not have been obvious over WO '675.

The secondary WO '131 and '709 references do not overcome the deficiencies of WO '675 for the reasons stated below.

WO '131 is directed to improving the bioavailability of poorly water-soluble drugs, like Compound (I), by forming a coprecipitate dispersion. WO '131, therefore, teaches forming a coprecipitate and *avoiding* the free form of a poorly water-soluble drug, like Compound (I), to improve dissolution of the drug. In addition, the examiner also states at page 5 of the Office Action that WO '131 "fails to teach the claimed particle sizes."

In contrast, the present claims recite incorporating Compound (I) of a certain particle into the formulation as a *free* drug. Rather than rendering the present claims obvious, after reading WO '131, a person skilled in the art would have had no motivation or incentive (a) to incorporate a free form of Compound (I) into a pharmaceutical formulation or (b) to provide a

free drug of the claimed particle size, let alone utilize *both* of these features. In fact, WO '131 actually teaches away from using a free form of Compound (I) and is silent with respect to particle size.

Seth et al. '709 also fails to cure the deficiencies of the combined teachings of WO '675 and WO '131. The '709 patent merely teaches fine particle size benzodiazepine drugs adsorbed onto a carrier. These drugs are substantially different from Compound (I). The '709 patent, at column 6, lines 40 through column 7, line 40 teaches how to adsorb the benzodiazepine drug onto a carrier by dissolution and precipitation. The adsorbed drug then is incorporated into a formulation. The '709 patent, however, fails to teach any formulations that would help overcome the deficiencies of WO '675 and WO '131, taken alone or in combination, to render the present claims obvious.

Accordingly, there is no teaching in the '709 patent that would lead a person skilled in the art to modify WO '675 and WO '131 in a manner to arrive at a presently claimed formulation as a whole.

In addition, the examiner misapplies applicants' incorporation of U.S. Patent No. 4,605,517 ('517) by reference. The '517 patent is incorporated by reference merely for the purpose of instructing persons reading the present specification how to measure particle size. See specification, page 8, lines 28-32. The '517 patent is not referenced for a method of preparing the present compositions. Preparation of the present compositions is illustrated in the examples, and applicants do not rely upon the method of U.S. Patent No. 4,605,517.

Furthermore, the examiner is focusing on the method of manufacturing the adsorbed drug disclosed in the '709 patent. Applicants are *not* claiming a method of manufacturing a pharmaceutical composition, but are claiming a composition. The presently claimed compositions are neither taught nor suggested by the combination of WO '675, WO '131, and the '709 patent. Accordingly, it is submitted that the rejection of the claims over the combination of WO '675, WO '131, and the '709 patent should be withdrawn.

Claims 1-26 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Nos. 10/031,531 and 10/031,463. Applicants traverse this rejection and submit that the rejection should be withdrawn.

In issuing an obviousness-type double patenting rejection, it is the *claims* of the present application that must be compared to the claims of U.S. Application Nos. 10/031,531 and 10/031,463. Applicants submit that in determining obviousness-type double patenting, the question to be considered is stated in *In re Vogel*, 164 U.S.P.Q. 619, 622 (CCPA 1970), i.e., "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" The CCPA goes on to indicate that, "In considering the question, the patent disclosure may not be used as prior art." For the reasons set forth below, the present obviousness-type double patenting rejection cannot be maintained.

As stated above, the present claims are directed to a stable pharmaceutical formulation that

demonstrates improved dissolution and improved *in vivo* absorption of Compound (I). The invention resides in the claimed formulation comprising an active compound provided as a free drug having a certain particle size in combination with ingredients, and amounts of ingredients, which achieve this result (see amended claim 1). Among the presently claimed features of the invention are a pharmaceutical formulation containing Compound (I) as a free drug, a small particle size of Compound (I), a solid formulation, a solid tablet, and a capsule containing dry, free-flowing particles of the formulation.

Application No. 10/031,531 is directed to capsules containing a solution or a dispersion of Compound (I). The formulations presently claimed in 10/031,531 directed to a suspension formulation of Compound (I) in a liquid, and are completely different from the present claims. The problem solved in 10/031,531 was to solubilize Compound (I) in a solution, or to provide a stable dispersion of Compound (I) in a liquid. Neither of these problems is considered in the present application, which is directed to *solid* (particulate) formulations containing Compound (I).

A person skilled in the art could not possibly arrive at a presently claimed composition after reading the claims of 10/031,531. A simple comparison of the present claims in 10/031,531 to the presently claimed formulations shows no relation between the compositions. The compositions in the 10/031,531 claims are totally different from the presently claimed formulations, and the 10/031,531 claims contain no teachings or suggestions that would lead a person

skilled in the art to modify the compositions claimed in 10/031,531 in a manner that would provide a presently claimed formulation as a whole regardless of whether the formulation is a capsule or solid. Moreover, the formulations are as fundamentally different as a solid formulation versus a liquid or dispersion formulation, before even considering the substantial differences between formulation ingredients.

The claims of application No. 10/031,463 are directed to Compound (I) in a reduced particle size. The present claims are directed to *formulations* containing free Compound (I) having a certain particle size, as well as other ingredients as recited in claim 1. The claims of application No. 10/031,463 merely recite the composition containing the small particle size of Compound (I) and one or more pharmaceutically acceptable carrier, diluent, or excipient. However, these claims fail to recite any *specific* carriers, diluents, or excipients as well as the form of formulation (tablet or capsule) as presently claimed, thus the 10/031,463 claims provide no teachings or suggestions that would lead a person skilled in the art to the presently claimed formulations as a whole.

In view of the above, it is submitted that the present claims are not obvious over the claims of application Nos. 10/031,531 and 10/031,463, which contain claims directed to inventions entirely different from the presently claimed invention. Therefore, it is submitted that the obviousness-type double patenting rejection of the present claims over the claims of application Nos. 10/031,531 and 10/031,463 is in error and should be withdrawn.

In response to the examiner's request to show that the inventions of the present application and application Nos. 10/031,531 and 10/031,463 were commonly aimed at the type of invention applicants provide the following assignment information.

Serial No.	Assignment Recordal	Provisional Application
10/031,464 (present application)	Reel 12877, Frame 177 May 8, 2002	60/146,924 filed April 3, 1999
10/031,463	Reel 13114, Frame 703 July 20, 2002	60/147,048 filed August 3, 1999
10/031,531	Reel 12818, Frame 640 April 15, 2002	60/146,924 filed August 3, 1999

The three applications are commonly owned by Lilly ICOS LLC. Applicants fail to see any interfering subject matter between the present claims and the present claims of 10/031,463 and 10/031,531. The recitation of application No. 10/031,151 in the Office Action is assumed to be a typographical error.

In summary, it is submitted that the present claims are in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

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Chicago, Illinois
September 24, 2004

BEST AVAILABLE COPY

Hawley's Condensed Chemical Dictionary

ELEVENTH EDITION

Revised by

N. Irving Sax
and
Richard J. Lewis, Sr.

VNR VAN NOSTRAND REINHOLD COMPANY
New York

Library of Congress Catalog Card Number: 86-23333
ISBN: 0-442-28097-1

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ISBN 0-442-28097-1

polymer, stereospecific. (stereoregular). A polymer whose molecular structure has a definite spatial arrangement, i.e., a fixed position in geometrical space for the constituent atoms and atomic groups comprising the molecular chain, rather than the random and varying arrangement that characterizes an amorphous polymer. Achievement of this specific steric (three-dimensional) structure (also called tacticity) requires use of special catalysts such as those developed by Ziegler and Natta about 1950. Such polymers are wholly or partially crystalline. Synthetic natural rubber, cis-polyisoprene, is an example of a stereospecific polymer made possible by this means. There are five types of stereospecific (or stereoregular) structures: cis, trans, isotactic, syndiotactic, and tritactic.
See also catalyst, stereospecific.

polymer, syndiotactic. See syndiotactic polymer.

polymer, synthetic. See polymer.

polymer, water-soluble. Any substance of high molecular weight that swells or dissolves in water at normal temperature. These fall into several groups, including natural, semisynthetic, and synthetic products. Their common property of water solubility makes them valuable for a wide variety of applications as thickeners, adhesives, coatings, food additives, textile sizing, etc.
See specific entries.
(1) *Natural*. This type is principally comprised of gums, which are complex carbohydrates of the sugar group. They occur as exudations of hardened sap on the bark of various tropical species of trees. All are strongly hydrophilic. Examples are arabic, tragacanth, karaya.
(2) *Semisynthetic*. This group (sometimes called water-soluble resins) includes such chemically treated natural polymers as carboxymethylcellulose, methylcellulose, and other cellulose ethers, as well as various kinds of modified starches (ethers and acetates).
(3) *Synthetic*. The principal members of this class are polyvinyl alcohol, ethylene oxide polymers, polyvinyl pyrrolidone, polyethyleneimine.

polymethacrylate resin. See acrylic resin, methyl methacrylate.

polymethylbenzene. See durene and pseudocumene, the two members of this group with some commercial production and use.

polymethylene polyphenylisocyanate. A polymer of diphenylmethane-4,4′ diisocyanate.

polymethylene wax. See wax, polymethylene.

poly-4-methylpentene-1.
Properties: High resistance to all chemicals except carbon tetrachloride and cyclohexane, excellent heat resistance, high clarity and light transmittance. Temperature limit 170C, d 0.83.
Use: Laboratory ware (beakers, graduates, etc.), electronic and hospital equipment; food packaging, especially types subject to high temperature such as trays for TV dinners, etc.; light reflectors.

poly(methyl vinyl ether). See polyvinyl methyl ether.

polymorphism. See allotropy.

polymyxin. CAS: 1406-11-7. Generic term for a series of antibiotic substances produced by strains of *Bacillus polymyxa*. Various polymyxins are differentiated by the letters A, B, C, D, and E. All are active against certain gram-negative bacteria. Polymyxin B is most used.
Properties: All are basic polypeptides, soluble in water; the hydrochlorides are soluble in water and methanol, insoluble in ether, acetone, chlorinated solvents, and hydrocarbons. Permissible food additives.
Use: Medicine (antibiotic), beer production.

polynuclear. Descriptive of an aromatic compound containing three or more closed rings, usually of the benzenoid type, e.g., sterols.
See also polycyclic, nucleus (3).

polyol. A polyhydric alcohol, i.e., one containing three or more hydroxyl groups. Those having three hydroxyl groups (trihydric) are glycerols, those with more than three are called sugar alcohols, with general formula $CH_2OH(CHOH)_n CH_2OH$, where n may be from 2 to 5. These react with aldehydes and ketones to form acetals and ketals.
See also alcohol, glycerol.

polyolefin. A class or group name for thermoplastic polymers derived from simple olefins, among the more important are polyethylene, polypropylene, polybutenes, polyisoprene and their copolymers. Many are produced in the form of fibers. This group comprises the largest tonnage of all thermoplastics produced.

polyorganosilicate graft polymer. An organoclay to which a monomer or an active polymer has been chemically bonded, often by the use of ionizing radiation. An example is the bonding of styrene to a polysilicate containing vinyl radicals, resulting in the growth of polystyrene chains from the surface of the silicate. Such complexes are stable to organic solvents. They have considerable use potential as ablative agents, draulic fluids.
See also organoclay,

"Polyox."[214] TM for ethylene oxide polym in the 100,000 to se
Use: Textile warp size, hair spray, toothpast film, adhesives.

polyoxadiazole. A pol C_2N_2O, prepared by mation from a chain ter) of polyisophthali high temperature tol made from it may be

polyoxamide. A nylon oxalic acid and diami

polyoxetane. See oxeta

polyoxyethylene. See

polyoxyethylene fatty ac

polyoxyethylene (40) n ene glycol stearate).
A mixture of the mo of mixed polyoxyethy ing free glycols. The n sented as: $H(OCH_2CH$ 40).
Properties: Waxy, light congealing range 39–4 hol, ether and aceton and vegetable oils.
Grade: USP.
Use: Ointments, emulsi tive.
See also polysorbate.

polyoxyethyleneoxyprop
A polymer of ethyle (ethylene oxide, propy
Use: Solvent.

polyoxyethylene (8) st
A mixture of the mor acid and mixed polyox average polymer lengt
Properties: Cream-colo solid at 25C, faint, fatty fatty taste. Soluble in t ethanol.
Use: Emulsifier in bake
See also polysorbate.

ABSTRACT

Formulations containing a PDE5 inhibitor, a water-soluble diluent, a lubricant, a hydrophilic binder, a disintegrant, and optional microcrystalline cellulose and/or a wetting agent, and their use in treating sexual dysfunction, are disclosed.

AMENDMENT TRANSMITTAL LETTER

Docket No. 29342/36230A

Application No.	Filing Date	Examiner	Art Unit
10/031,464-Conf. #6930	April 29, 2002	Not Yet Assigned	1615

Applicant(s): Peter L. Oren et al.

Invention: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims	88	- 26 =	62	x 18.00	1,116.00
Independent Claims	2	- 3 =		x	
Multiple Dependent Claims (check if applicable)			[x]		290.00
Other fee (please specify):	Extension for response within first month				110.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					1,516.00

[x] Large Entity [ ] Small Entity

[ ] No additional fee is required for this amendment.

[ ] Please charge Deposit Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

[x] A check in the amount of $ 1,516.00 to cover the filing fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[x] The Director is hereby authorized to charge and credit Deposit Account No. 13-2855 as described below. A duplicate copy of this sheet is enclosed.

[x] Credit any overpayment.

[x] Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.

James J. Napoli
Attorney Reg. No.: 32,361

Dated: September 24, 2004

MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: September 24, 2004 Signature: _____ (James J. Napoli)

PTO/SB/17 (10-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,516.00

Complete if Known	
Application Number	10/031,464-Conf. #6930
Filing Date	April 29, 2002
First Named Inventor	Peter L. Oren
Examiner Name	Not Yet Assigned
Art Unit	1615
Attorney Docket No.	29342/36230A

METHOD OF PAYMENT *(check all that apply)*

☒ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number: 13-2855

Deposit Account Name: MARSHALL, GERSTEIN & BORUN LLP

The Director is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims	88	-26** =	62	x	18.00	=	1,116.00
Independent Claims	2	-3** =		x		=	
Multiple Dependent					290.00	=	290.00

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 1,406.00

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	110.00
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 110.00

SUBMITTED BY					(Complete *(if applicable)*)
Name (Print/Type)	James J. Napoli	*Registration No. (Attorney/Agent)*	32,361	*Telephone*	(312) 474-6300
Signature	James J. Napoli			*Date*	September 24, 2004

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: September 24, 2004 Signature: James J. Napoli (James J. Napoli)

09/28/2004 EAREGAY1 00000036 10031464
03 FC:1251 110.00 OP

Barbara Campbell
National Stage Processing
(703) 305-3031

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number
10/031464

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	26 minus 20=	* 6
INDEPENDENT CLAIMS	1 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	84
X$ 9=		OR	X$18=	108
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 88	Minus	** 26	= 62
Independent	* 2	Minus	*** 3	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☑

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	1116
X42=		OR	X84=	—
+140=		OR	+280=	290
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	1406

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
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.

9/27/04

National Stage Processing (703) 305-3031

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO. 10/031464 | 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		1		1		
5		1		1		
6		1		1		
7		1		1		
8		1		1		
9		1		1		
10		1		1		
11		1		1		
12		1		1		
13		1		1		
14		1		1		
15		1		1		
16		1		1		
17		1		—		
18		1		1		
19		1		1		
20		1		1		
21		1		1		
22		1		1		
23		1		1		
24		1		1		
25		1		1		
26		1		—		
27		1	Corrected			
28				1		
29				1		
30				1		
31				1		
32				1		
33				1		
34				1		
35				28		
36				28		
37			1			
38						
39						
40						
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46						
47						
48						
49						
50						
TOTAL IND.		↓	2	↓		↓
TOTAL DEP.			1 − 86			
TOTAL CLAIMS			88			

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
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55						
56						
57						
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90						
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96						
97						
98						
99						
100						
TOTAL IND.		↓		↓		↓
TOTAL DEP.						
TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS

Barbara Campbell
National Stage Processing
(703) 305-3631

FORM PTO-1340 (REV. 3-78)

Barbara Campbell
National Stage Processing
(703) 305-3631

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

4743 7590 03/03/2005

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.**	**Applicant(s)**	
	10/031,464	OREN ET AL.	
	Examiner	**Art Unit**	
	Lakshmi S. Channavajjala	1615	

-- 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) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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 27 September 2004.

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) 1-16,18-25 and 28-37 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) 1-16,18-25 and 28-37 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-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment and remarks dated 9-27-04 is acknowledged.

Claims 17 and 26-27 were canceled. New claims 28-36 have been added. Claims 1-16, 18-25 and 28-37 are pending.

In view of the amendment presented, the following new rejection is applied to the pending claims:

Newly presented composition claims are also included in he rejection for the reasons mentioned below:

Claim Rejections - 35 USC § 103

Claims 1-16, 18-25 and 28-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03675 (Daung) in view of WO 96/38131 (Butler) and US 4,721,709 to Seth et al (Seth).

Daung teaches the claimed beta-carboline compounds and compositions containing the compounds, as also acknowledged by applicants on page 2 of the instant application. Daung specifically discloses teaches instant preferred compound (instant specification, page 3, lines 28-30) for treating conditions where inhibition of PDE5 is beneficial (see page 3, lines 24-25, lines 30-32 and is also referred to as compound A). On page 12, lines 11-12, Daung teaches that the compounds a and B are prepared as different dosage forms and in particular, Table B shows a tablet prepared by wet granulation, where in the tablet composition contains beta-carboline drug as active agent and other excipients such as polyvinylpyrrolidone, PEG, Polysorbate 80, magnesium stearate, crosscaramellose sodium, and microcrystalline cellulose, which

read on the instant claimed binder, diluent, wetting agent, lubricant and disintegrant respectively. Instant dependent claims specifically recite the excipients of Table B of Daung. With respect to the percentages of active ingredients and the excipients claimed, the total weight of the composition of tablet in Table B is 500 mg. A calculation of the proportion of each ingredient in Table 2 reads on the instant claimed percentages. With respect to the claimed "free drug", Daung does not teach an intimately embedded drug in a polymeric co-precipitate and hence meets the definition of instant "free drug" (instant page 5, lines 24-27). Instead, Daung only teaches direct compression or wet granulation followed by compression to prepare the tablets (pages 12-14).

Daung fails to teach the claimed particulates and sizes of particles, exact or the percentages of diluent (claim 5), lubricant (claim 8), binder (claim 10), and the claimed amounts of drug in tablet (claims 22, 23) and capsule (claim 25). However as acknowledged by applicants, Daung teaches the active agent and also for the same purposes i.e., as a 5PDE inhibitor. Further Daung teaches the same pharmaceutical compositions containing the same active compound and excipients, as claimed, in the form of tablets and capsules. Accordingly, optimizing the amounts of art recognized excipients such as binder, lubricant, optimizing the amount of active compound with an expectation to achieve the appropriate dosage form as well the desired therapeutic efficiency of the drug would have been within the scope of a skilled artisan because Daung suggests optimizing the amounts of drug in the range of 0.5 to 800 mg per day

and also employing the suitable excipients depending on the route of administration (page 5).

Butler teaches pharmaceutical compositions comprising beta-carboline compounds (abstract, page 4, lines 15-21). The specific beta-carboline compound taught by Butler is the same as that claimed in the instant invention. Further, Butler teaches that the above are poorly soluble in nature. Butler teaches solid dispersions but fails to teach the claimed particle sizes.

Seth teaches pharmaceutical composition containing poorly water-soluble drugs and a method of preparing the same. The method of Seth is practically applicable to all water insoluble drugs and comprises the steps of providing dry powder of the insoluble drug that is adsorbed on to a carrier such as starch or cellulose and is characterized in that the drug is present particulate form and at least 95% of the drug particles have a mean size of less than 15 microns (col. 4, lines 44-53, col. 3, lines 60-67), which is in the same range as claimed. Seth teaches that the drug particles are closely associated with the carrier and details the method of preparing the formulation in col. 6, lines 1-39. Further, Seth teaches preparation of various dosage forms such as tablets, capsules etc., with the above prepared formulation (col. 8). Examiner notes that instant specification refers to US patent 4,605,517 by incorporation for the preparation of the instant drug formulation. It is noted that the above patent also recites the same method of preparation as that of Seth. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare drug formulations of beta-carboline of Daung containing the excipients such as lubricants, wetting agents

etc., by the process of Seth i.e., particulate drug adsorbed on to excipients or carrier and compressing into tablets because Seth teaches that the conventional methods of jet milling or pin milling employed in drug preparation result in slow dissolution and absorption, (col. 2, lines 1-20) and that their method avoids the disadvantages of agglomeration and poor flow seen in the conventional methods. Accordingly, the expected result would be an increased dissolution of beta-carboline and hence increased bioavailability without agglomeration.

Double Patenting

Claims 1-16, 18-25 and 28-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 8, 9, 12-21 and 22-24 of copending Application No. 10/031,531and over claims 1-9 and14-16 of copending Application No. 10/031,463. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claimed composition containing a free drug, beta-carboline together with excipients and also composition comprising particulate form of the drug is also claimed in the above patent applications. US application 10/031,531 the composition of the instant claims in the form of capsules, which is reads on the claimed subject matter of instant claim 25. Further, method of treating specific disorders using the above composition by '131 anticipates instant method of treatment. Accordingly, claims of application 10/031,531 anticipate instant claims.

US application 10/031,463 claims a free drug particulate form of beta-carboline, compositions containing the free drug, a method of treating a patient in need thereof. The copending claims also recite particle sizes, carriers or excipients, which read on the instant dependent claims. Accordingly, the copending claims directed specifically to particulate beta-carboline compound, composition containing particulate compound anticipate instant broadly recited pharmaceutical compositions and method claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 9-27-04 have been fully considered but they are not persuasive.

In response to applicants' amendment to instant claims, examiner has withdrawn the following rejections:

Rejection of claims 1-4, 6, 7, 9, 11-16 and 26 as being anticipated by WO (Daugan).

Rejection of claims 5, 8, 10, 19 and 22-25 as being obvious over Daugan. However, instant claims are now rejected as being obvious over Daung in view of Butler (WO '131) and Seth et al ('709) (see above).

Applicants argue that WO fails to teach the particle size of compound I in claim 1. It is argued that instant compounds are highly water-insoluble that are not easy to formulate into pharmaceutical formulations and that an intensive research resulted in

providing a stable composition of the instant compounds with improved dissolution and in vivo absorption. Applicants admits that WO '131 is directed to improving the bioavailability of poorly-soluble drugs, like compound I, but states that is achieved by co-precipitate dispersion and avoids a free form of poorly-water soluble drug. However, WO '131 nowhere compares and teaches away from preparing a free drug formulation as opposed to the preferred co-precipitate. Besides, instant specification states that instant formulation preferably contains a free drug form of the compound claimed, but fails to provide any unexpected results with the free drug form versus a co-precipitate form. The rejection clearly cites the teachings of WO '131 to show that the compounds claimed are known to be poorly soluble and not for the claimed particle sizes. Accordingly, the argument that the WO '131 fails to teach the particle sizes is moot.

Applicants argue that '709 fail to cure the deficiencies of the combined teachings of WO '675 and WO '131 because the patent merely teaches fine particle benzodiazepine drugs, which are different from the claimed compound. While it is true that instant claims do not recite a method of manufacturing adsorbed drug, as taught by '709 or US 4,605,517, the reference '709 teaches employing particulate material to improve dissolution and also avoid the problems of agglomeration and poor flow. Thus, the motivation to employ a particulate compound in the teachings of Daung comes from the teaching that the compounds are poorly soluble (WO '131) and that preparing fine particles of a poorly soluble drug improves the dissolution (Seth, '709).

Double patenting Rejection:

Applicants argue that patent disclosure may not be used as a prior art in determining if claims in any application are mere obvious variation of an invention. While applicants admit that instant application claims encompass a tablet, capsule or other solid formulation, applicants argue that the claims of 10/031,531 is a suspension formulation of a compound in a liquid. However, applicants' arguments are not persuasive because instant claims does not state the composition is solid and therefore the claimed formulation is generic to various dosage forms such as tablets, soft or hard capsules.

Applicants argue that the claims of application no. 10/031,463 merely recite the composition and not any specific carriers, diluents or excipients, as claimed in the instant. However, applicants' arguments are not persuasive because merely adding a suitable carrier or excipient to a known pharmaceutical composition is within the scope of a one of an ordinary skill in the art of preparing pharmaceutical formulations. Examiner notes that instant new claim 37 does not specify any carrier or diluent etc.

Conclusion

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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. 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).

Lakshmi S Channavajjala
Examiner
Art Unit 1615

February 26, 2005

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/031,464	OREN ET AL.
Examiner	**Art Unit**
Lakshmi S. Channavajjala	1615

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

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RESPONSE UNDER 37 C.F.R. 116
EXPEDITED PROCEDURE
EXAMINING ART UNIT 1615

PATENT--NO FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to:
Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dated: **June 2, 2005**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

AMENDMENT "B" AFTER FINAL UNDER 37 C.F.R. §1.116

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

Sir:

In response to the Office Action of March 3, 2005 (Final), please amend the above-identified application as follows. Reconsideration and allowance of the application are respectfully requested.

AF
IFW

AMENDMENT TRANSMITTAL LETTER

Docket No. 29342/36230A

Application No.	Filing Date	Examiner	Art Unit
10/031,464-Conf. #6930	April 29, 2002	L. S. Channavajjala	1615

Applicant(s): Peter L. Oren et al.

Invention: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims	82	- 88 =		x	
Independent Claims	2	- 3 =		x	
Multiple Dependent Claims (check if applicable)		☐			
Other fee (please specify):					
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					0.00

☒ Large Entity ☐ Small Entity

☒ No additional fee is required for this amendment.

☐ Please charge Deposit Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

☐ A check in the amount of $ _____ to cover the filing fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge and credit Deposit Account No. 13-2855 as described below. A duplicate copy of this sheet is enclosed.

☒ Credit any overpayment.

☒ Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.

James J. Napoli

Dated: June 2, 2005

James J. Napoli
Attorney Reg. No.: 32,361

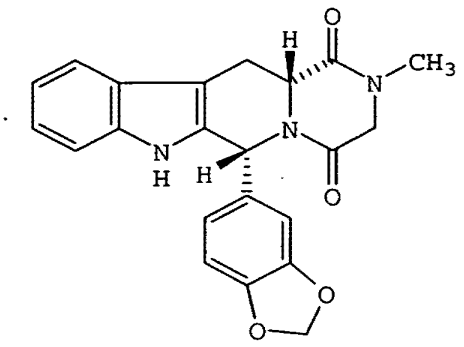
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: June 2, 2005 Signature: James J. Napoli (James J. Napoli)

IN THE CLAIMS:

1. (Currently amended) A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles have a particle size of less than about 40 microns; about 50% to about 80%, by weight, of a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

2. (Original) The formulation of claim 1 further comprising microcrystalline cellulose.

3. (Original) The formulation of claim 1 further comprising a wetting agent.

4. (Original) The formulation of claim 1 wherein the active compound is present in an amount of about 0.5% to about 10% by weight.

5. (Cancelled)

6. (Original) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of a sugar, a polysaccharide, a polyol, a cyclodextrin, and mixtures thereof.

7. (Previously presented) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of lactose, sucrose, dextrose, a dextrate, a maltodextrin, mannitol, xylitol, sorbitol, a cyclodextrin, and mixtures thereof.

8. (Original) The formulation of claim 1 wherein the lubricant is present in an amount of about 0.25% to about 2% by weight.

9. (Original) The formulation of claim 1 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, hydrogenated vegetable oils, and mixtures thereof.

10. (Original) The formulation of claim 1 wherein the hydrophilic binder is present in an amount of about 1% to about 5% by weight.

11. (Original) The formulation of claim 1 wherein the cellulose derivative is selected from the group consisting of hydroxypropylcellulose, hydroxypropyl methylcellulose, and mixtures thereof.

12. (Original) The formulation of claim 1 wherein the disintegrant is present in an amount of about 3% to about 10% by weight.

13. (Original) The formulation of claim 2 wherein the microcrystalline cellulose is present in an amount of about 5% to about 40% by weight.

14. (Original) The formulation of claim 3 wherein the wetting agent is present in an amount of 0.1% to about 5% by weight.

15. (Original) The formulation of claim 14 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, docusate sodium, ethoxylated castor oil, a polyglycolyzed glyceride, an acetylated monoglyceride, a sorbitan fatty acid ester, a poloxamer, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene, a monoglyceride and ethoxylated derivatives thereof, a diglyceride and ethoxylated derivatives thereof, and mixtures thereof.

16. (Previously presented) The formulation of claim 15 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, polysorbate 80, and a mixture thereof.

17. (Cancelled)

18. (Original) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 10 microns.

19. (Original) The formulation of claim 1 comprising:

(a) about 1% to about 4% by weight of the active compound;

(b) about 50% to about 75% by weight lactose;

(c) about 0.25% to about 2% by weight magnesium stearate;

(d) about 1% to about 5% by weight hydroxypropyl cellulose; and

(e) about 3% to about 10% by weight croscarmellose sodium.

20. (Original) The formulation of claim 18 further comprising about 5% to about 40% by weight microcrystalline cellulose.

21. (Original) The formulation of claim 18 further comprising about 0.1% to about 5% by weight sodium lauryl sulfate.

22. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 20 mg per tablet.

23. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 to about 15 mg per tablet.

24. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 mg per tablet.

25. (Original) A capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles, wherein the active compound is present in an amount of about 1 to about 20 mg per capsule.

26. (Cancelled)

27. (Cancelled)

28. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 30 microns.

29. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 25 microns.

30. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 15 microns.

31. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 10 mg per tablet.

32. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 5 mg per tablet.

33. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 2.5 mg per tablet.

34. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 20 mg per tablet.

35. (Currently amended) A method of treating sexual dysfunction in a patient in need thereof comprising administering to the patient an effective amount of a formulation or a tablet according to of any one of claims 1 through ~~25~~ 4, 6 through 16, 18 through 25, or ~~claims~~ 28 through 30.

36. (Previously presented) The method of claim 35 wherein the sexual dysfunction is male erectile dysfunction.

37. (Cancelled)

REMARKS

Claims 1-16, 18-25 and 28-37 are pending in the application. Claims 5 and 37 have been cancelled by this amendment. Claims 17, 26, and 27 were cancelled previously. Therefore, claims 1-4, 6-16, 18-25, and 28-36 are at issue.

This amendment is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b) in order to present the rejected claims in a better form for allowance or appeal. This amendment was not presented earlier because the rejection under 35 U.S.C. §103 is new grounds of rejection. Applicants also believed, and still believe, that the obviousness-type double patenting rejection was fully addressed in Amendment "A" filed September 27, 2004. This amendment should be entered because it places the application in better form for allowance or appeal, and the amendment does not require further searching or present any new issues.

Claim 1 has been amended to incorporate the features of originally filed, and now-cancelled, claim 5. Claim 35 has been amended to correct the dependency of the claim.

I. Request for Withdrawal of Final Rejection

Applicants respectfully request a withdrawal of the finality of the rejection because the present rejection under 35 U.S.C. §103 is a new grounds of rejection that was *not* necessitated by an amendment. Under M.P.E.P. 706.07(a), a final rejection is not

proper when the examiner introduces a new ground of rejection that is neither necessitated by applicants' amendment of the claims nor based on information submitted in an IDS. In particular, in Amendment "A," claim 1 was amended to insert the features of originally filed claim 17. The issuance of a final rejection, therefore, is premature because the examiner issued a *new* ground of rejection on a claim already before the examiner. Accordingly, it is submitted that the final rejection is not in accordance with the well-established practice under M.P.E.P. and, thus, should be withdrawn.

II. Rejection Under 35 U.S.C. §103

Claims 1-16, 18-25, and 28-37 stand rejected under 35 U.S.C. §103 as being unpatentable over WO 97/03675 (WO '675) in view of WO 96/38131 (WO '131 and U.S. Patent No. 4,721,709 ('709). In view of the amendments to the claims and for the reasons set forth below, it is submitted that this rejection should be withdrawn.

The present invention is directed to a pharmaceutical formulation, which exhibits unexpected and surprising results in therapeutic delivery of Compound (A) through enhanced dosage uniformity, stability, and bioavailability. As a result, the present invention achieves a rapid onset of a therapeutic effect, which has been identified as a problem involving the β-carboline (see specification, page 1, lines 16-19; page 2, line 24 through page 3; page 7, lines 21-28). The unexpected and surprising results of the present formu-

lation are achieved because of (i) the presence of Compound (A) as a free drug comprising a particle size of less than about 40 microns *and* (ii) the presence and amounts of other important formulation ingredients, such as a water-soluble diluent, a lubricant, a hydrophilic binder and a disintegrant. The present application specifically discloses that "the particle size of the active compound also has been found to enhance the bioavailability and handling of the present formulation" (see Specification page 8, lines 14-23). The effects and importance of other formulation ingredients are also disclosed in detail, for example, at page 9, lines 24-33; and page 10, lines 16-23. Furthermore, the present invention provides a formulation having improved stability over prior formulations, in addition to improved dissolution and *in vivo* adsorption (page 12, line 32 through page 12, line 2).

Briefly, WO '675 discloses a method treating male erectile dysfunction using Compound (A) and a tablet containing Compound (A), and in particular tablet formulation B.1. at page 13. However, as stated by the examiner, WO '675 fails to teach or suggest use of a free drug form of Compound (A), the particle size of Compound (A), *or* the specifically claimed formulation, let alone all three features.

As stated above, the presently claimed formulations provide a stable composition that effectively delivers the claimed compound (i.e., Compound (A)) *in vivo*. Because Compound (A) is a highly water-insoluble drug, its formulation into a pharmaceutical composition that effectively delivers the drug is not straightfor-

ward. As a result of applicants' investigation, a pharmaceutical composition that is surprisingly physically stable, and that demonstrates improved dissolution and *in vivo* absorption has been achieved.

The differences between WO '675 and the present claims are substantial. First, the presently claimed formulation contains Compound (A) as a free drug in a claimed particle size, whereas WO '675 fails to teach or suggest either of these features of Compound (A). These features, together with the other claimed formulation ingredients, provide the new and unexpected benefits achieved by the presently claimed invention described above.

In addition, the presently claimed formulations, as a whole, are substantially different from the formulations disclosed in WO '675. The following table compares a composition disclosed in WO '675, and relied upon by the examiner, to the presently claimed composition.

Ingredient	**WO '675**[1)]	**Claim 1**
1. Compound (A)	10% w/w	present
2. polyvinyl pyrrolidone (PVP)	30% w/w	present
3. polyethylene glycol (PEG)	10% w/w	not present
4. polysorbate 80	2% w/w	present (claim 3)
5. magnesium stearate colloidal silicon dioxide	0.5% w/w 0.5% w/w	present
6. croscarmellose sodium	5% w/w	present
7. microcrystalline cellulose	42% w/w	present (claim 2)
8. water-soluble diluent	not present	50-80% w/w

[1)] Formulation B.1. at page 13 of WO '675.

The compositions of WO '675 and claim 1 (or a claim depending therefrom) both include Compound (A), a

wetting agent (e.g., polysorbate 80), a lubricant (magnesium stearate and colloidal silicon dioxide), croscarmellose sodium, and microcrystalline cellulose.

However, the compositions then greatly differ. For example,

(a) the composition of WO '675 contains PEG. Claims 1 and 6 recite a water-soluble diluent, including a polyol, which by definition does not include PEG. See the diluent examples in the specification, and see the definition of a "polyol" previously provided with Amendment "A."

(b) the composition of WO '675 contains 10% w/w PEG, which even if considered a water-soluble diluent, is far below the 50-85% w/w recited in claim 1 for the water-soluble diluent. Furthermore, the water-soluble diluents of the present invention are solids (see claim 7) to effect tablet manufacture. Also, see the specification at page 9, lines 24-30. PEG would not serve in this capacity.

(c) the composition of WO '675 contains 30% w/w PVP. Claim 10 recites 1-5% w/w of a hydrophilic binder, e.g,. PVP. Furthermore, WO '675 fails to teach or suggest a cellulose derivative as the hydrophilic binder.

In view of the above, WO '675 fails to teach the "same" pharmaceutical compositions containing the same active compound and excipients, as asserted by the examiner, and WO '675 has failed to teach or suggest the present invention as a whole. Accordingly, it is submitted that the present invention as a whole would not have been obvious over WO '675.

Moreover, the nonobviousness of the present invention is further demonstrated by the claimed features that the examiner acknowledges are *not* disclosed or suggested in WO '675, i.e., particle size of Compound (A), percentages of ingredients, and amounts of drug in the tablet or capsule (see Office Action, page 3, lines 11-13). The examiner also made an erroneous assumption in reasoning by concluding that WO '675 teaches a free form of Compound (A) because WO '675 fails to disclose an imbedded form of Compound (A). This basis of rejection and reasoning cannot be maintained since it is not in accordance with well-established standard of obviousness test. WO '675 is silent with respect to the form of Compound (A) in the formulation, and thus simply did not disclose this aspect of the present invention.

The secondary WO '131 and '709 references do not overcome the deficiencies of WO '675 for the reasons stated below.

WO '131 is directed to, *and limited to*, improving the bioavailability of poorly water-soluble drugs, like Compound (A), by forming a coprecipitate dispersion. WO '131 explains the problems associated with poorly water-soluble drugs in the free form, e.g., poor bioavailability, and teaches that solid dispersions of a poorly water-soluble drug may overcome these problems. WO '131 then discloses a coprecipitation technique that overcomes the problems associated with poorly water-soluble drugs in the free form and prior solid dispersions. See WO '131, pages 1-4.

WO '131, therefore, merely teaches forming a coprecipitate, and thereby *avoiding* the free form of a poorly water-soluble drug, like Compound (A), to improve dissolution of the drug. WO '131 provides absolutely no teaching or motivation to utilize a free form of Compound (A) in a pharmaceutical formulation to achieve enhanced bioavailability and stability, but rather teaches away from using the free form of Compound (A) to achieve what has achieved by the presently claimed formulation. In fact, it is the problem encountered using a free form of a poorly water soluble drug that WO '131 addresses and attempts to solve.

Although WO '131 provides various examples of pharmaceutical formulations, these formulations contain Compound (A) as a coprecipitate, which again is substantially different from the presently claimed formulations. Therefore, contrary to the examiner's contention, the specific β-carboline coprecipitate compound taught in WO '131 is *different from* the presently claimed free form of Compound (A) in the claimed particle size. In addition, the examiner acknowledges at page 4 of the Office Action that WO '131 "fails to teach the claimed particle sizes," and further, WO '131 fails to suggest using the claimed particle size. Finally, the formulations disclosed in WO '131 at pages 16-19 are substantially different from the presently claimed compositions as a whole.

In view of the above, the cited references, alone or in combination, fail to provide a person skilled in the art a motivation or incentive (a) to incorporate a free form of Compound (A) into a pharma-

ceutical formulation or (b) to provide a free drug of the claimed particle size, let alone utilize *both* of these features, with any reasonable expectation of improving dissolutions and *in vivo* absorption of Compound (A).

Seth et al. '709 also fails to cure the deficiencies of the combined teachings of WO '675 and WO '131. The '709 patent merely teaches fine particle size benzodiazepine drugs *adsorbed* onto a carrier. According to '709 patent, the critical feature of the Seth invention is directed to "the fine particle size of the absorbed hydrophobic drug" (see column 6, lines 13-14). In addition, as stated by the examiner, the "method of Seth comprises the steps of providing dry powder of the insoluble drug that is adsorbed onto a carrier" and "Seth teaches that the drug particles are closely associated with the carrier" (Office Action, page 4). This is in direct contrast to the presently claimed feature of a *free* particle form of Compound (A). The '709 patent simply fails to teach or suggest a free form of the drug, but rather teaches the *necessity and criticality* of adsorbing the drug onto a carrier (see '709 patent, column 4, lines 44-52, for example).

In addition to failing to teach or suggest using a free form of a drug in a formulation, the formulations provided in the '709 patent at columns 9 and 10 are substantially different from the claimed formulations as a whole, and provide no suggestions with respect to modifying formulation ingredients to arrive at the presently claimed formulation. The '709 patent,

therefore, not only fails to teach or suggest a free form of a drug, but also fails to teach or suggest any formulations or formulation modifications that would help overcome the deficiencies of WO '675 and WO '131, taken alone or in combination, to render the present claims obvious. Furthermore, the examiner misapplies applicants' incorporation of U.S. Patent No. 4,605,517 in the present specification ('517) by reference. As specifically stated in the present specification at page 8, lines 28-32, the '517 patent is incorporated by reference *merely* for the purpose of instructing persons reading the present specification how to measure particle size, and, thus, the '517 patent is not referenced for a method of preparing the present formulations. Preparation of the present formulations is illustrated in the examples of the present application, and, thus, do not rely upon the method of U.S. Patent No. 4,605,517.

In summary, for the reasons stated above, the present invention, as a whole, is neither taught nor suggested by any of the cited references, alone or in combination. Accordingly, it is respectfully submitted that the rejection under 35 U.S.C. §103 should be withdrawn.

III. Rejection Under Obviousness-Type Double Patenting

Claims 1-16, 18-25, and 28-37 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Nos. 10/031,531 and 10/031,463. Appli-

cants traverse this rejection and submit that the rejection should be withdrawn.

In issuing an obviousness-type double patenting rejection, it is the *claims* of the present application that must be compared to the *claims* of U.S. Application Nos. 10/031,531 and 10/031,463. Applicants submit that in determining obviousness-type double patenting, the question to be considered is stated in *In re Vogel*, 164 U.S.P.Q. 619, 622 (CCPA 1970), i.e., "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" The CCPA goes on to indicate that, "In considering the question, the patent disclosure may not be used as prior art." For the reasons set forth below, the present obviousness-type double patenting rejection cannot be maintained.

As stated above, the present claims are directed to a pharmaceutical formulation that demonstrates improved dissolution, stability, and *in vivo* absorption of Compound (A). The invention resides in the claimed formulation comprising an active compound provided as a free drug having a certain particle size in combination with additional claimed ingredients, and claimed amounts of ingredients, which achieve this result (see amended claim 1). Among the presently claimed features of the invention are a pharmaceutical formulation containing Compound (A) as a free drug, a small particle size of Compound (A), a solid formulation, a solid tablet, and a capsule containing dry, free-flowing particles of the formulation.

Application No. 10/031,531 is directed to capsules containing a solution or a dispersion of Compound (A). Application No. 10/031,531 has been allowed, and has issued as U.S. patent No. 6,841,167 ('167). All claims in the '167 patent recite a suspension formulation of Compound (A) in specifically claimed solvents and a specifically claimed suspending agent, and are limited to capsules. The subject matter of the allowed '167 claims is completely different from the present claims and patentably distinct, which are directed to *particulate* formulation, tablets containing the formulation and capsules containing dry, free flowing particles of the formulation (see original claim 25). The problem solved in the '167 patent was to solubilize Compound (A) in a solution, or to provide a stable dispersion of Compound (A) in a liquid. Neither of these problems is even addressed or considered in the present application, which is directed to *solid* (particulate) formulations containing Compound (A).

A person skilled in the art could not possibly arrive at a presently claimed composition based on the claims of the '167 patent because a comparison of the '167 patent claims to the presently claimed formulations shows no relation between the compositions. The compositions of the '167 patent claims are totally different from the presently claimed formulations, and the '167 patent claims contain no teachings or suggestions that would lead a person skilled in the art to modify the compositions claimed in '167 patent in a manner that would provide a presently claimed particulate formulation regardless of whether the formu-

lation is a capsule or a tablet. Moreover, the formulations are as fundamentally different as a solid formulation versus a dispersion formulation, before even considering the substantial differences between formulation ingredients as a whole. In addition, the amendment to claim 1 reciting a particulate formulation overcomes the examiner's reasoning at page 8 of the Office Action for maintaining the obviousness-type double patent rejection over the '167 patent.

The claims of application No. 10/031,463, now U.S. Patent No. 6,821,975 ('975), are directed to Compound (A) in a reduced particle size. The present claims are directed to *formulations* containing free Compound (A) having a claimed particle size, *as well as* the ingredients recited in claim 1. The claims of the '975 patent only recite the composition containing the small particle size of Compound (A) and one or more pharmaceutically acceptable carrier, diluent, or excipient. However, these claims fail to recite any *specific* carriers, diluents, or excipients, or the form of formulation (tablet or capsule) as presently claimed. Thus, the '975 patent claims provide no teachings or suggestions that would lead a person skilled in the art to the presently claimed formulations *as a whole.*

Additionally, in applying the test set out in *In re Vogel*, it is submitted that the present claims are patentably distinct and not obvious over the claims of U.S. Patent Nos. 6,841,167 and 6,821,975, which contain claims directed to inventions entirely different from the presently claimed invention. Therefore, it is

submitted that the obviousness-type double patenting rejection of the present claims over the claims of U.S. Patent Nos. 6,841,167 and 6,821,975 is in error and should be withdrawn.

Furthermore, applicants clearly are not attempting to claim related subject matter in order to extend the patent terms of the '167 patent or the '975 patent, which the doctrine of obviousness-type double patenting is intended to present. See, e.g., *In re Kaplan*, 229 U.S.P.Q. 278 (Fed. Cir. 1986). In this case, claims issuing from the present application presumptively will terminate on April 26, 2020 (i.e., twenty years from the filing date of the PCT application upon which the present application is based). The '167 patent claims likewise will terminate on April 26, 2020 because it also is based on a PCT application filed on April 26, 2000 and received no patent term extension. The '975 patent will expire on November 18, 2020, (twenty years after the filing date of the PCT application upon which the patent is based (August 1, 2000) plus a 110-day patent term extension), which is *after* the termination date of any patent issuing from the present application. Accordingly, it cannot be argued that applicants are attempting to extend the patent term of an invention claimed in the '167 and '975 patents, and thus the very reason formed the basis for obviousness-type rejection is vitiated by the above fact.

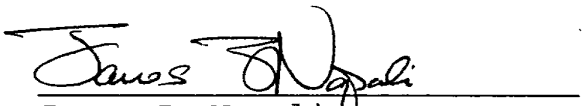
In summary, it is submitted that the present claims are in a form and scope for allowance. An early

and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

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June 2, 2005

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

4743 7590 06/21/2005

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/031,464	**Applicant(s)** OREN ET AL.	
	Examiner Lakshmi S. Channavajjala	**Art Unit** 1615	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 June 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-16,18-25 and 28-37*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

S.O.

Continuation of 3. NOTE: because the change in the percentage range of the dileunt requires further consideration. Applicants' request for withdrawal of finality has been considered but not found persuasive because, in response to the non-final rejection, applicants canceled calim 17 and amended origianl claim 1 to incorporate the limitations of claims 17, which necessitated the withdrawal of the rejection of claims under 35 USC 102(b). However, in view of the amendemnt, amended claim 1 was rejected under 35 USC 103. Thus, the rejection of origianl claim as being obvious was necessitated by the amendment.Thus, the finality of the previous action was proper. Further, newly added claims, in response to the non-final rejection of 3-3-05, were dependent on claim 1 and were hence rejected along with claim 1 as being obvious.

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Discussed with GS Kishore	6/16/2005	LC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper 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

Dated: **July 5, 2005**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

AMENDMENT "B" AFTER FINAL UNDER 37 C.F.R. §1.116

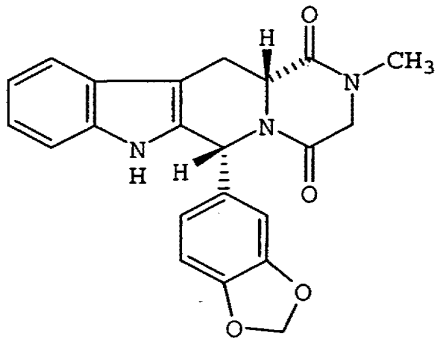
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action of March 3, 2005 (Final), please amend the above-identified application as follows. Reconsideration and allowance of the application are respectfully requested.

IN THE CLAIMS:

1. (Currently amended) A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles have a particle size of less than about 40 microns; about 50% to about 85%, by weight, of a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

2. (Original) The formulation of claim 1 further comprising microcrystalline cellulose.

3. (Original) The formulation of claim 1 further comprising a wetting agent.

4. (Original) The formulation of claim 1 wherein the active compound is present in an amount of about 0.5% to about 10% by weight.

5. (Cancelled)

6. (Original) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of a sugar, a polysaccharide, a polyol, a cyclodextrin, and mixtures thereof.

7. (Previously presented) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of lactose, sucrose, dextrose, a dextrate, a maltodextrin, mannitol, xylitol, sorbitol, a cyclodextrin, and mixtures thereof.

8. (Original) The formulation of claim 1 wherein the lubricant is present in an amount of about 0.25% to about 2% by weight.

9. (Original) The formulation of claim 1 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, hydrogenated vegetable oils, and mixtures thereof.

10. (Original) The formulation of claim 1 wherein the hydrophilic binder is present in an amount of about 1% to about 5% by weight.

11. (Original) The formulation of claim 1 wherein the cellulose derivative is selected from the group consisting of hydroxypropylcellulose, hydroxypropyl methylcellulose, and mixtures thereof.

12. (Original) The formulation of claim 1 wherein the disintegrant is present in an amount of about 3% to about 10% by weight.

13. (Original) The formulation of claim 2 wherein the microcrystalline cellulose is present in an amount of about 5% to about 40% by weight.

14. (Original) The formulation of claim 3 wherein the wetting agent is present in an amount of 0.1% to about 5% by weight.

15. (Original) The formulation of claim 14 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, docusate sodium, ethoxylated castor oil, a polyglycolyzed glyceride, an acetylated monoglyceride, a sorbitan fatty acid ester, a poloxamer, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene, a monoglyceride and ethoxylated derivatives thereof, a diglyceride and ethoxylated derivatives thereof, and mixtures thereof.

16. (Previously presented) The formulation of claim 15 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, polysorbate 80, and a mixture thereof.

17. (Cancelled)

18. (Original) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 10 microns.

19. (Original) The formulation of claim 1 comprising:

(a) about 1% to about 4% by weight of the active compound;

(b) about 50% to about 75% by weight lactose;

(c) about 0.25% to about 2% by weight magnesium stearate;

(d) about 1% to about 5% by weight hydroxypropyl cellulose; and

(e) about 3% to about 10% by weight croscarmellose sodium.

20. (Original) The formulation of claim 18 further comprising about 5% to about 40% by weight microcrystalline cellulose.

21. (Original) The formulation of claim 18 further comprising about 0.1% to about 5% by weight sodium lauryl sulfate.

22. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 20 mg per tablet.

23. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 to about 15 mg per tablet.

24. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 mg per tablet.

25. (Original) A capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles, wherein the active compound is present in an amount of about 1 to about 20 mg per capsule.

26. (Cancelled)

27. (Cancelled)

28. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 30 microns.

29. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 25 microns.

30. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 15 microns.

31. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 10 mg per tablet.

32. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 5 mg per tablet.

33. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 2.5 mg per tablet.

34. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 20 mg per tablet.

35. (Currently amended) A method of treating sexual dysfunction in a patient in need thereof comprising administering to the patient an effective amount of a formulation or a tablet according to of any one of claims 1 through ~~25~~ 4, 6 through 16, 18 through 25, or ~~claims~~ 28 through 30.

36. (Previously presented) The method of claim 35 wherein the sexual dysfunction is male erectile dysfunction.

37. (Cancelled)

REMARKS

Claims 1-16, 18-25 and 28-37 are pending in the application. Claims 5 and 37 have been cancelled by this amendment. Claims 17, 26, and 27 were cancelled previously. Therefore, claims 1-4, 6-16, 18-25, and 28-36 are at issue.

This amendment is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b) in order to present the rejected claims in a better form for allowance or appeal. This amendment was not presented earlier because the rejection under 35 U.S.C. §103 is new grounds of rejection. Applicants also believed, and still believe, that the obviousness-type double patenting rejection was fully addressed in Amendment "A" filed September 27, 2004. This amendment should be entered because it places the application in better form for allowance or appeal, and the amendment does not require further searching or present any new issues.

Claim 1 has been amended to incorporate the features of originally filed, and now-cancelled, claim 5. Claim 35 has been amended to correct the dependency of the claim.

I. Request for Withdrawal of Final Rejection

Applicants respectfully request a withdrawal of the finality of the rejection because the present rejection under 35 U.S.C. §103 is a new grounds of rejection that was *not* necessitated by an amendment. Under M.P.E.P. 706.07(a), a final rejection is not

proper when the examiner introduces a new ground of rejection that is neither necessitated by applicants' amendment of the claims nor based on information submitted in an IDS. In particular, in Amendment "A," claim 1 was amended to insert the features of originally filed claim 17. The issuance of a final rejection, therefore, is premature because the examiner issued a *new* ground of rejection on a claim already before the examiner. Accordingly, it is submitted that the final rejection is not in accordance with the well-established practice under M.P.E.P. and, thus, should be withdrawn.

II. Rejection Under 35 U.S.C. §103

Claims 1-16, 18-25, and 28-37 stand rejected under 35 U.S.C. §103 as being unpatentable over WO 97/03675 (WO '675) in view of WO 96/38131 (WO '131 and U.S. Patent No. 4,721,709 ('709). In view of the amendments to the claims and for the reasons set forth below, it is submitted that this rejection should be withdrawn.

The present invention is directed to a pharmaceutical formulation, which exhibits unexpected and surprising results in therapeutic delivery of Compound (A) through enhanced dosage uniformity, stability, and bioavailability. As a result, the present invention achieves a rapid onset of a therapeutic effect, which has been identified as a problem involving the β-carboline (see specification, page 1, lines 16-19; page 2, line 24 through page 3; page 7, lines 21-28). The unexpected and surprising results of the present formu-

lation are achieved because of (i) the presence of Compound (A) as a free drug comprising a particle size of less than about 40 microns *and* (ii) the presence and amounts of other important formulation ingredients, such as a water-soluble diluent, a lubricant, a hydrophilic binder and a disintegrant. The present application specifically discloses that "the particle size of the active compound also has been found to enhance the bioavailability and handling of the present formulation" (see Specification page 8, lines 14-23). The effects and importance of other formulation ingredients are also disclosed in detail, for example, at page 9, lines 24-33; and page 10, lines 16-23. Furthermore, the present invention provides a formulation having improved stability over prior formulations, in addition to improved dissolution and *in vivo* adsorption (page 12, line 32 through page 12, line 2).

Briefly, WO '675 discloses a method treating male erectile dysfunction using Compound (A) and a tablet containing Compound (A), and in particular tablet formulation B.1. at page 13. However, as stated by the examiner, WO '675 fails to teach or suggest use of a free drug form of Compound (A), the particle size of Compound (A), *or* the specifically claimed formulation, let alone all three features.

As stated above, the presently claimed formulations provide a stable composition that effectively delivers the claimed compound (i.e., Compound (A)) *in vivo*. Because Compound (A) is a highly water-insoluble drug, its formulation into a pharmaceutical composition that effectively delivers the drug is not straightfor-

ward. As a result of applicants' investigation, a pharmaceutical composition that is surprisingly physically stable, and that demonstrates improved dissolution and *in vivo* absorption has been achieved.

The differences between WO '675 and the present claims are substantial. First, the presently claimed formulation contains Compound (A) as a free drug in a claimed particle size, whereas WO '675 fails to teach or suggest either of these features of Compound (A). These features, together with the other claimed formulation ingredients, provide the new and unexpected benefits achieved by the presently claimed invention described above.

In addition, the presently claimed formulations, as a whole, are substantially different from the formulations disclosed in WO '675. The following table compares a composition disclosed in WO '675, and relied upon by the examiner, to the presently claimed composition.

Ingredient	**WO '675**[1)]	**Claim 1**
1. Compound (A)	10% w/w	present
2. polyvinyl pyrrolidone (PVP)	30% w/w	present
3. polyethylene glycol (PEG)	10% w/w	not present
4. polysorbate 80	2% w/w	present (claim 3)
5. magnesium stearate colloidal silicon dioxide	0.5% w/w 0.5% w/w	present
6. croscarmellose sodium	5% w/w	present
7. microcrystalline cellulose	42% w/w	present (claim 2)
8. water-soluble diluent	not present	50-80% w/w

[1)] Formulation B.1. at page 13 of WO '675.

The compositions of WO '675 and claim 1 (or a claim depending therefrom) both include Compound (A), a

wetting agent (e.g., polysorbate 80), a lubricant (magnesium stearate and colloidal silicon dioxide), croscarmellose sodium, and microcrystalline cellulose.

However, the compositions then greatly differ. For example,

(a) the composition of WO '675 contains PEG. Claims 1 and 6 recite a water-soluble diluent, including a polyol, which by definition does not include PEG. See the diluent examples in the specification, and see the definition of a "polyol" previously provided with Amendment "A."

(b) the composition of WO '675 contains 10% w/w PEG, which even if considered a water-soluble diluent, is far below the 50-85% w/w recited in claim 1 for the water-soluble diluent. Furthermore, the water-soluble diluents of the present invention are solids (see claim 7) to effect tablet manufacture. Also, see the specification at page 9, lines 24-30. PEG would not serve in this capacity.

(c) the composition of WO '675 contains 30% w/w PVP. Claim 10 recites 1-5% w/w of a hydrophilic binder, e.g,. PVP. Furthermore, WO '675 fails to teach or suggest a cellulose derivative as the hydrophilic binder.

In view of the above, WO '675 fails to teach the "same" pharmaceutical compositions containing the same active compound and excipients, as asserted by the examiner, and WO '675 has failed to teach or suggest the present invention as a whole. Accordingly, it is submitted that the present invention as a whole would not have been obvious over WO '675.

Moreover, the nonobviousness of the present invention is further demonstrated by the claimed features that the examiner acknowledges are *not* disclosed or suggested in WO '675, i.e., particle size of Compound (A), percentages of ingredients, and amounts of drug in the tablet or capsule (see Office Action, page 3, lines 11-13). The examiner also made an erroneous assumption in reasoning by concluding that WO '675 teaches a free form of Compound (A) because WO '675 fails to disclose an imbedded form of Compound (A). This basis of rejection and reasoning cannot be maintained since it is not in accordance with well-established standard of obviousness test. WO '675 is silent with respect to the form of Compound (A) in the formulation, and thus simply did not disclose this aspect of the present invention.

The secondary WO '131 and '709 references do not overcome the deficiencies of WO '675 for the reasons stated below.

WO '131 is directed to, *and limited to*, improving the bioavailability of poorly water-soluble drugs, like Compound (A), by forming a coprecipitate dispersion. WO '131 explains the problems associated with poorly water-soluble drugs in the free form, e.g., poor bioavailability, and teaches that solid dispersions of a poorly water-soluble drug may overcome these problems. WO '131 then discloses a coprecipitation technique that overcomes the problems associated with poorly water-soluble drugs in the free form and prior solid dispersions. See WO '131, pages 1-4.

WO '131, therefore, merely teaches forming a coprecipitate, and thereby *avoiding* the free form of a poorly water-soluble drug, like Compound (A), to improve dissolution of the drug. WO '131 provides absolutely no teaching or motivation to utilize a free form of Compound (A) in a pharmaceutical formulation to achieve enhanced bioavailability and stability, but rather teaches away from using the free form of Compound (A) to achieve what has achieved by the presently claimed formulation. In fact, it is the problem encountered using a free form of a poorly water soluble drug that WO '131 addresses and attempts to solve.

Although WO '131 provides various examples of pharmaceutical formulations, these formulations contain Compound (A) as a coprecipitate, which again is substantially different from the presently claimed formulations. Therefore, contrary to the examiner's contention, the specific β-carboline coprecipitate compound taught in WO '131 is *different from* the presently claimed free form of Compound (A) in the claimed particle size. In addition, the examiner acknowledges at page 4 of the Office Action that WO '131 "fails to teach the claimed particle sizes," and further, WO '131 fails to suggest using the claimed particle size. Finally, the formulations disclosed in WO '131 at pages 16-19 are substantially different from the presently claimed compositions as a whole.

In view of the above, the cited references, alone or in combination, fail to provide a person skilled in the art a motivation or incentive (a) to incorporate a free form of Compound (A) into a pharma-

ceutical formulation or (b) to provide a free drug of the claimed particle size, let alone utilize *both* of these features, with any reasonable expectation of improving dissolutions and *in vivo* absorption of Compound (A).

Seth et al. '709 also fails to cure the deficiencies of the combined teachings of WO '675 and WO '131. The '709 patent merely teaches fine particle size benzodiazepine drugs *adsorbed* onto a carrier. According to '709 patent, the critical feature of the Seth invention is directed to "the fine particle size of the absorbed hydrophobic drug" (see column 6, lines 13-14). In addition, as stated by the examiner, the "method of Seth comprises the steps of providing dry powder of the insoluble drug that is adsorbed onto a carrier" and "Seth teaches that the drug particles are closely associated with the carrier" (Office Action, page 4). This is in direct contrast to the presently claimed feature of a *free* particle form of Compound (A). The '709 patent simply fails to teach or suggest a free form of the drug, but rather teaches the *necessity and criticality* of adsorbing the drug onto a carrier (see '709 patent, column 4, lines 44-52, for example).

In addition to failing to teach or suggest using a free form of a drug in a formulation, the formulations provided in the '709 patent at columns 9 and 10 are substantially different from the claimed formulations as a whole, and provide no suggestions with respect to modifying formulation ingredients to arrive at the presently claimed formulation. The '709 patent,

therefore, not only fails to teach or suggest a free form of a drug, but also fails to teach or suggest any formulations or formulation modifications that would help overcome the deficiencies of WO '675 and WO '131, taken alone or in combination, to render the present claims obvious. Furthermore, the examiner misapplies applicants' incorporation of U.S. Patent No. 4,605,517 in the present specification ('517) by reference. As specifically stated in the present specification at page 8, lines 28-32, the '517 patent is incorporated by reference *merely* for the purpose of instructing persons reading the present specification how to measure particle size, and, thus, the '517 patent is not referenced for a method of preparing the present formulations. Preparation of the present formulations is illustrated in the examples of the present application, and, thus, do not rely upon the method of U.S. Patent No. 4,605,517.

In summary, for the reasons stated above, the present invention, as a whole, is neither taught nor suggested by any of the cited references, alone or in combination. Accordingly, it is respectfully submitted that the rejection under 35 U.S.C. §103 should be withdrawn.

III. Rejection Under Obviousness-Type Double Patenting

Claims 1-16, 18-25, and 28-37 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Nos. 10/031,531 and 10/031,463. Appli-

cants traverse this rejection and submit that the rejection should be withdrawn.

In issuing an obviousness-type double patenting rejection, it is the *claims* of the present application that must be compared to the *claims* of U.S. Application Nos. 10/031,531 and 10/031,463. Applicants submit that in determining obviousness-type double patenting, the question to be considered is stated in *In re Vogel*, 164 U.S.P.Q. 619, 622 (CCPA 1970), i.e., "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" The CCPA goes on to indicate that, "In considering the question, the patent disclosure may not be used as prior art." For the reasons set forth below, the present obviousness-type double patenting rejection cannot be maintained.

As stated above, the present claims are directed to a pharmaceutical formulation that demonstrates improved dissolution, stability, and *in vivo* absorption of Compound (A). The invention resides in the claimed formulation comprising an active compound provided as a free drug having a certain particle size in combination with additional claimed ingredients, and claimed amounts of ingredients, which achieve this result (see amended claim 1). Among the presently claimed features of the invention are a pharmaceutical formulation containing Compound (A) as a free drug, a small particle size of Compound (A), a solid formulation, a solid tablet, and a capsule containing dry, free-flowing particles of the formulation.

Application No. 10/031,531 is directed to capsules containing a solution or a dispersion of Compound (A). Application No. 10/031,531 has been allowed, and has issued as U.S. patent No. 6,841,167 ('167). All claims in the '167 patent recite a suspension formulation of Compound (A) in specifically claimed solvents and a specifically claimed suspending agent, and are limited to capsules. The subject matter of the allowed '167 claims is completely different from the present claims and patentably distinct, which are directed to *particulate* formulation, tablets containing the formulation and capsules containing dry, free flowing particles of the formulation (see original claim 25). The problem solved in the '167 patent was to solubilize Compound (A) in a solution, or to provide a stable dispersion of Compound (A) in a liquid. Neither of these problems is even addressed or considered in the present application, which is directed to *solid* (particulate) formulations containing Compound (A).

A person skilled in the art could not possibly arrive at a presently claimed composition based on the claims of the '167 patent because a comparison of the '167 patent claims to the presently claimed formulations shows no relation between the compositions. The compositions of the '167 patent claims are totally different from the presently claimed formulations, and the '167 patent claims contain no teachings or suggestions that would lead a person skilled in the art to modify the compositions claimed in '167 patent in a manner that would provide a presently claimed particulate formulation regardless of whether the formu-

lation is a capsule or a tablet. Moreover, the formulations are as fundamentally different as a solid formulation versus a dispersion formulation, before even considering the substantial differences between formulation ingredients as a whole. In addition, the amendment to claim 1 reciting a particulate formulation overcomes the examiner's reasoning at page 8 of the Office Action for maintaining the obviousness-type double patent rejection over the '167 patent.

The claims of application No. 10/031,463, now U.S. Patent No. 6,821,975 ('975), are directed to Compound (A) in a reduced particle size. The present claims are directed to *formulations* containing free Compound (A) having a claimed particle size, *as well as* the ingredients recited in claim 1. The claims of the '975 patent only recite the composition containing the small particle size of Compound (A) and one or more pharmaceutically acceptable carrier, diluent, or excipient. However, these claims fail to recite any *specific* carriers, diluents, or excipients, or the form of formulation (tablet or capsule) as presently claimed. Thus, the '975 patent claims provide no teachings or suggestions that would lead a person skilled in the art to the presently claimed formulations *as a whole*.

Additionally, in applying the test set out in *In re Vogel*, it is submitted that the present claims are patentably distinct and not obvious over the claims of U.S. Patent Nos. 6,841,167 and 6,821,975, which contain claims directed to inventions entirely different from the presently claimed invention. Therefore, it is

submitted that the obviousness-type double patenting rejection of the present claims over the claims of U.S. Patent Nos. 6,841,167 and 6,821,975 is in error and should be withdrawn.

Furthermore, applicants clearly are not attempting to claim related subject matter in order to extend the patent terms of the '167 patent or the '975 patent, which the doctrine of obviousness-type double patenting is intended to present. See, e.g., *In re Kaplan*, 229 U.S.P.Q. 278 (Fed. Cir. 1986). In this case, claims issuing from the present application presumptively will terminate on April 26, 2020 (i.e., twenty years from the filing date of the PCT application upon which the present application is based). The '167 patent claims likewise will terminate on April 26, 2020 because it also is based on a PCT application filed on April 26, 2000 and received no patent term extension. The '975 patent will expire on November 18, 2020, (twenty years after the filing date of the PCT application upon which the patent is based (August 1, 2000) plus a 110-day patent term extension), which is *after* the termination date of any patent issuing from the present application. Accordingly, it cannot be argued that applicants are attempting to extend the patent term of an invention claimed in the '167 and '975 patents, and thus the very reason formed the basis for obviousness-type rejection is vitiated by the above fact.

In summary, it is submitted that the present claims are in a form and scope for allowance. An early

and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

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(Registration No. 32,361)
Attorneys for Applicants
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(312) 474-6300

Chicago, Illinois
July 5, 2005

RCE

PTO/SB/30 (04-05)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Request For Continued Examination (RCE) Transmittal

Address to:
MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/031,464-Conf. #6930
Filing Date	April 29, 2002
First Named Inventor	Peter L. Oren
Art Unit	1615
Examiner Name	L. S. Channavajjala
Attorney Docket Number	29342/36230A

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.

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. [X] Enclosed
     - i. [X] Amendment/Reply
     - ii. [ ] Affidavit(s)/Declaration(s)
     - iii. [ ] Information Disclosure Statement (IDS)
     - iv. [X] Other postcard
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. [X] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments to Deposit Account No. 13-2855 . I have enclosed a duplicate copy of this sheet.
     - i. [X] RCE fee required under 37 CFR 1.17(e)
     - ii. [X] Extension of time fee (37 CFR 1.136 and 1.17) (one month - $120.00)
     - iii. [ ] Other _____
   - b. [X] Check in the amount of $ 910.00 enclosed
   - c. [ ] Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	James J. Napoli	Date	July 5, 2005
Name (Print/Type)	James J. Napoli	Registration No.	32,361

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: July 5, 2005 Signature: James J. Napoli (James J. Napoli)

07/12/2005 ZJUHAR1 00000032 10031464
01 FC:1801 790.00 OP

PTO/SB/22 (12-04)
Approved for use through 7/31/2006. 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) FY 2005 (Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)	Docket Number (Optional) 29342/36230A
Application Number 10/031,464-Conf. #6930	Filed April 29, 2002
For BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS	
Art Unit 1615	Examiner L. S. Channavajjala

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	
[x]	One month (37 CFR 1.17(a)(1))	$120	$60	$ 120.00
[ ]	Two months (37 CFR 1.17(a)(2))	$450	$225	$
[ ]	Three months (37 CFR 1.17(a)(3))	$1020	$510	$
[ ]	Four months (37 CFR 1.17(a)(4))	$1590	$795	$
[ ]	Five months (37 CFR 1.17(a)(5))	$2160	$1080	$

[ ] Applicant claims small entity status. See 37 CFR 1.27.

[x] 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.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 13-2855 . I have enclosed a duplicate copy of this sheet.

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 _____

[x] attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 32,361 .

James J. Napoli
Signature

July 5, 2005
Date

James J. Napoli
Typed or printed name

(312) 474-6300
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.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: July 5, 2005 Signature: James J. Napoli (James J. Napoli)

07/12/2005 ZJUHAR1 00000032 10031464

02 FC:1251 120.00 OP

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number
10/031464

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS *		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	26 minus 20=	* 6
INDEPENDENT CLAIMS	1 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	88
X$ 9=		OR	X$18=	108
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 88	Minus	** 26	= 62
Independent	* 2	Minus	*** 3	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☑

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	1116
X42=		OR	X84=	—
+140=		OR	+280=	290
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	1406

5/27/04

11/05

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 78	Minus	** 88	=
Independent	* 1	Minus	*** 2	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

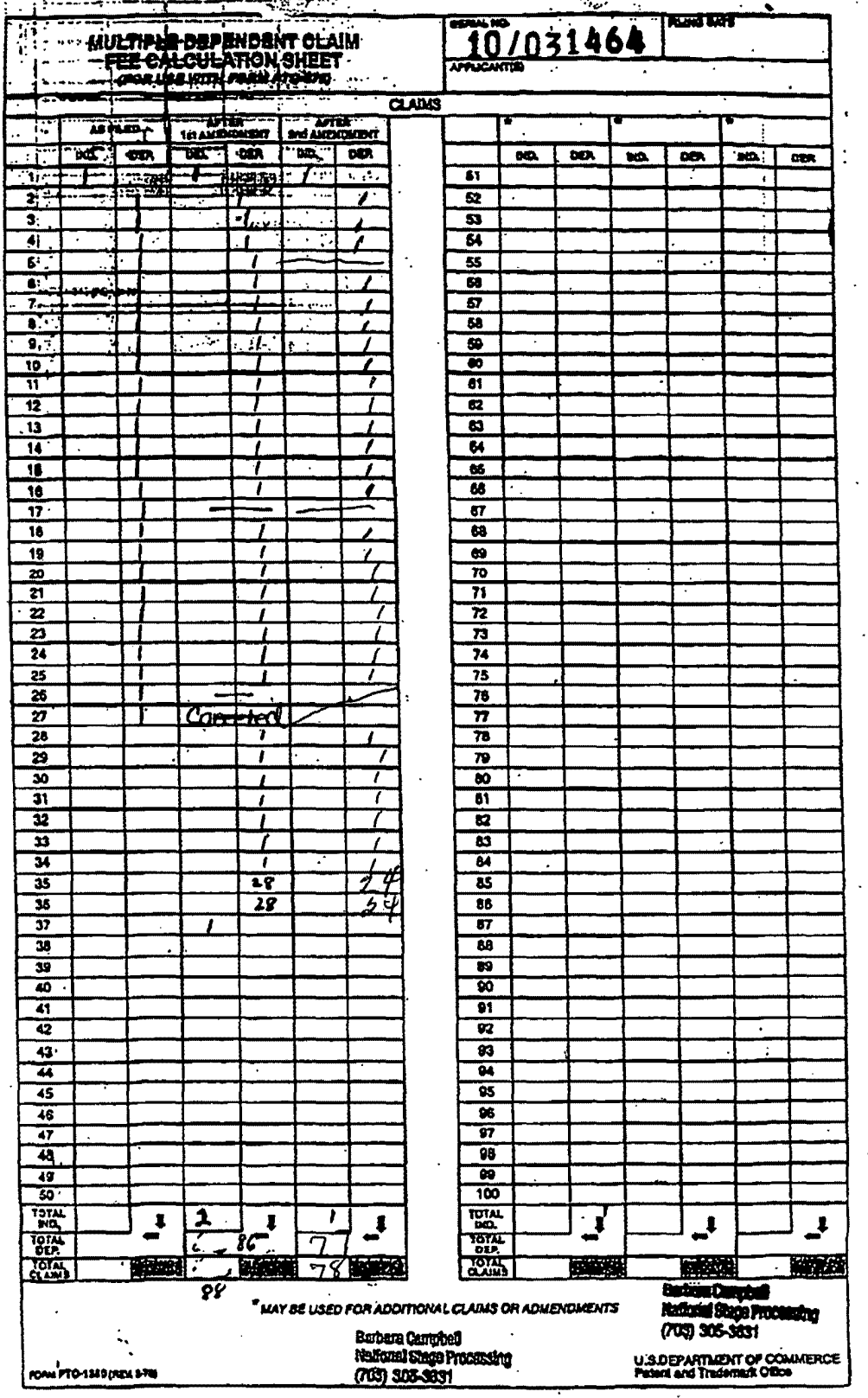
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
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

SERIAL NO. 10/031464

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1						
2						/
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27			Corrected			
28				/		/
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TOTAL DEP.			86	7		
TOTAL CLAIMS			88	78		

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	IND.	DEP.	IND.	DEP.	IND.	DEP.
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100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

Barbara Campbell
National Stage Processing
(703) 305-3831

FORM PTO-1360 (REV. 5-96)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Barbara Campbell
National Stage Processing
(703) 305-3831

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Sunday, September 18, 2005

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=OR	
☐	L6	(solvent or diluent) same (peg or polyethylene adj glycol) same (lactose or sorbitol or mannitol or sucrose or dextrose or dextrate or maltodextrin or xylitol or cyclodextrin) same (water adj insoluble or hydrophobic or lippophilic) adj3 (drug or active or medicament)	139
☐	L5	(solvent or diluent) same (peg or polyethylene adj glycol) same (lactose or sorbitol or mannitol or sucrose or dextrose or dextrate or maltodextrin or xylitol or cyclodextrin) and (water adj insoluble or hydrophobic or lippophilic) adj3 (drug or active or medicament)	1250
☐	L4	(solvent or diluent) same (peg or polyethylene adj glycol) same (lactose or sorbitol or mannitol or sucrose or dextrose or dextrate or maltodextrin or xylitol or cyclodextrin) and (drug or tablet or capsule)	18965
☐	L3	L1 and (rapid or quick or fast) adj5 (dissolution or dissolving)	17
☐	L2	L1 and (rapid or quick or fast) adj5 (dissolution or dissolving) same (drug or active or medicament or therapeutic)	2
☐	L1	water adj soluble adj3 (solvent or diluent) same (peg or polyethylene adj glycol) same (lactose or sorbitol or mannitol or sucrose or dextrose or dextrate or maltodextrin or xylitol or cyclodextrin)	91

END OF SEARCH HISTORY

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

4743 7590 09/21/2005

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- 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) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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 *11 July 2005*.

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) *1-4,6-16,18-25 and 28-36* 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) *1-4,6-16,18-25 and 28-36* 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-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

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 7-11-05 has been entered.

Claims 1-4, 6-16, 18-25 and 28-36 are pending in the instant application.

Claim Rejections - 35 USC § 103

Claims 1-4, 6-16, 18-25 and 28-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03675 (Daung) in view of WO 96/38131 (Butler) and US 4,721,709 to Seth et al (Seth).

Daung teaches the claimed beta-carboline compounds and compositions containing the compounds, as also acknowledged by applicants on page 2 of the instant application. Daung specifically discloses teaches instant preferred compound (instant specification, page 3, lines 28-30) for treating conditions where inhibition of PDE5 is beneficial (see page 3, lines 24-25, lines 30-32 and is also referred to as compound A). On page 12, lines 11-12, Daung teaches that the compounds a and B are prepared as different dosage forms and in particular, Table B shows a tablet prepared by wet granulation, where in the tablet composition contains beta-carboline drug as active agent and other excipients such as polyvinylpyrrolidone, PEG, Polysorbate 80,

magnesium stearate, crosscaramellose sodium, and microcrystalline cellulose, which read on the instant claimed binder, diluent, wetting agent, lubricant and disintegrant respectively. Instant dependent claims specifically recite the excipients of Table B of Daung. With respect to the percentages of active ingredients and the excipients claimed, the total weight of the composition of tablet in Table B is 500 mg. A calculation of the proportion of each ingredient in Table 2 reads on the instant claimed percentages. With respect to the claimed "free drug", Daung does not teach an intimately embedded drug in a polymeric co-precipitate and hence meets the definition of instant "free drug" (instant page 5, lines 24-27). Instead, Daung only teaches direct compression or wet granulation followed by compression to prepare the tablets (pages 12-14).

Daung fails to teach the claimed particulates and sizes of particles, exact or the percentages of diluent (claim 5), lubricant (claim 8), binder (claim 10), and the claimed amounts of drug in tablet (claims 22, 23) and capsule (claim 25). However as acknowledged by applicants, Daung teaches the active agent and also for the same purposes i.e., as a 5PDE inhibitor. Further Daung teaches the pharmaceutical compositions containing the same active compound and excipients, as claimed, in the form of tablets and capsules. Accordingly, optimizing the amounts of art recognized excipients such as binder, lubricant, optimizing the amount of active compound with an expectation to achieve the appropriate dosage form as well the desired therapeutic efficiency of the drug would have been within the scope of a skilled artisan because Daung suggests optimizing the amounts of drug in the range of 0.5 to 800 mg per day

and also employing the suitable excipients depending on the route of administration (page 5).

Butler teaches pharmaceutical compositions comprising beta-carboline compounds (abstract, page 4, lines 15-21). The specific beta-carboline compound taught by Butler is the same as that claimed in the instant invention. Further, Butler teaches that the above are poorly soluble in nature. Butler teaches solid dispersions but fails to teach the claimed particle sizes.

Seth teaches pharmaceutical composition containing poorly water-soluble drugs and a method of preparing the same. The method of Seth is practically applicable to all water insoluble drugs and comprises the steps of providing dry powder of the insoluble drug that is adsorbed on to a carrier such as starch or cellulose and is characterized in that the drug is present particulate form and at least 95% of the drug particles have a mean size of less than 15 microns (col. 4, lines 44-53, col. 3, lines 60-67), which is in the same range as claimed. Seth teaches that the drug particles are closely associated with the carrier and details the method of preparing the formulation in col. 6, lines 1-39. Further, Seth teaches preparation of various dosage forms such as tablets, capsules etc., with the above prepared formulation (col. 8). Examiner notes that instant specification refers to US patent 4,605,517 by incorporation for the preparation of the instant drug formulation. It is noted that the above patent also recites the same method of preparation as that of Seth. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare drug formulations of beta-carboline of Daung containing the excipients such as lubricants, wetting agents

etc., by the process of Seth i.e., particulate drug adsorbed on to excipients or carrier and compressing into tablets because Seth teaches that the conventional methods of jet milling or pin milling employed in drug preparation result in slow dissolution and absorption, (col. 2, lines 1-20) and that their method avoids the disadvantages of agglomeration and poor flow seen in the conventional methods. Accordingly, the expected result would be an increased dissolution of beta-carboline and hence increased bioavailability without agglomeration.

Double Patenting

Claims 1-4, 6-16, 18-25 and 28-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U. S. Patent No. 6,821,975. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claimed composition containing a free drug, beta-carboline together with excipients and also composition comprising particulate form of the drug is also claimed in the above patent applications. The patent claims a free drug particulate form of beta-carboline, compositions containing the free drug, a method of treating a patient in need thereof. The copending claims also recite particle sizes and broadly recite carriers or excipients, as in instant claims. While the patent fails to list the specific diluents and other excipients of the instant claims, choosing an appropriate solvents, diluents, and other

art recognized pharmaceutical excipients with an expectation to prepare a desired dosage form would have been obvious for one of an ordinary skill in the art.

Response to Arguments

Applicant's arguments filed 7-11-05 have been fully considered but they are not persuasive.

35 U.S.C. 103(a) REJECTION:

Applicants argue that instant composition exhibits unexpected and surprising results in therapeutic delivery of compound A through enhanced dosage uniformity, stability ad bioavailability and thus rapid onset of a therapeutic effect. This unexpected result, applicants state, is due to the compound A as a free drug, the particle size and the presence of ingredients such as water-soluble diluent, lubricant etc. Applicants argue that WO '675 fails to teach the above features. Applicants compared the difference between instant composition and that of WO '675 and argue that the PEG of the reference, by definition is not included in the list of "polyols" as suitable water-soluble diluent. However, instant claim 1 only recites a water-soluble diluent and does not exclude PEG of WO '675. Besides, PEG is defined as a water-soluble compound (see the definition of PEG, as given in Hawley's Condensed Chemical Dictionary, 1997, page 898). Applicants' argue that the amount of PEG in the reference is much lower in amounts than that claimed in the application. However, absent any unexpected results with respect to the high amounts of PEG, it is examiner's position that the optimizing the amount of a diluent so as to achieve the desired dilution would have been within the

scope of a skilled artisan. In response to the argument that the reference does not teach PVP, table 2 (on page 13) clearly describes PVP. While applicants argue that WO '675 is silent regarding the free form of a compound, examiner clearly explained, based on applicants own definition of "free base" that the reference meets the claim term. Further, the burden is shifted to applicants to establish that the compound is in fact not a free drug.

Applicants argue that WO '131 explains the problems associated with free forms of water-soluble drugs and overcomes the problem with co-precipitation. Therefore, applicants conclude that WO '131 teaches away from a free base of the drug. However, WO '131 nowhere compares and teaches away from preparing a free drug formulation as opposed to the preferred co-precipitate. The rejection clearly cites the teachings of WO '131 to show that the compounds claimed are known to be poorly soluble and not for the claimed particle sizes. '709 teach employing particulate material to improve dissolution and also avoid the problems of agglomeration and poor flow. Thus, the motivation to employ a particulate compound in the teachings of Daung comes from the teaching that the compounds are poorly soluble (WO '131) and that preparing fine particles of a poorly soluble drug improves the dissolution (Seth, '709).

DOUBLE PATENTING REJECTION:

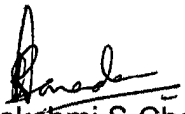
Applicants argue U.S. Patent No. 6,821,975 ('975) is directed to a compound and the composition claim only mentions diluents, excipients or a tablet or a capsule, as in the instant composition. However, applicants' argument is not persuasive because

instant claim also broadly recites the excipients, diluents etc., but does not state any specific compounds. Accordingly, the argument is moot.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. 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).



Lakshmi S Channavajjala
Examiner
Art Unit 1615

September 18, 2005

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination
	10/031,464	OREN ET AL.
	Examiner	Art Unit
	Lakshmi S. Channavajjala	1615

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
west- all databases (search attached)	9/18/2005	LC

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/031,464	OREN ET AL.
Examiner	**Art Unit**
Lakshmi S. Channavajjala	1615

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
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PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	) I hereby certify that this
PETER L. OREN ET AL.	) paper is being deposited
	) with the United States
Serial No.: 10/031,464	) Postal Service with
	) sufficient postage, as
Filed: April 29, 2002	) first class mail, in an
	) envelope addressed to:
For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**	) Mail Stop Amendment
	) Commissioner for Patents
	) P.O. Box 1450
	) Alexandria, VA 22313-1450
Attorney Docket No. 29342/36230A	)
	) Dated: **December 21, 2005**
Group Art Unit: 1615	)
	)
Examiner: L. Channavajjala	) James J. Napoli
	) Registration No. 32,361
	) Attorney for Applicants

AMENDMENT "C"

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

Sir:

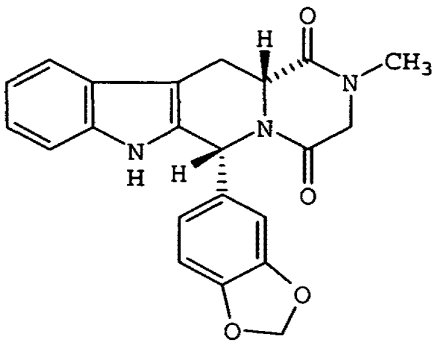
In response to the Office Action of September 21, 2005, please amend the above-identified application as follows. Reconsideration and allowance of the application are respectfully requested.

12/30/2005 DTESSEM1 00000110 10031464
01 FC:1051 130.00 OP

Void date: 12/30/2005 LWONDIM1
12/30/2005 DTESSEM1 00000110 10031464
01 FC:1051 130.00 OP

IN THE CLAIMS:

1. (Previously presented) A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles have a particle size of less than about 40 microns; about 50% to about 85%, by weight, of a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

2. (Original) The formulation of claim 1 further comprising microcrystalline cellulose.

3. (Original) The formulation of claim 1 further comprising a wetting agent.

4. (Original) The formulation of claim 1 wherein the active compound is present in an amount of about 0.5% to about 10% by weight.

5. (Cancelled)

6. (Original) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of a sugar, a polysaccharide, a polyol, a cyclodextrin, and mixtures thereof.

7. (Previously presented) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of lactose, sucrose, dextrose, a dextrate, a maltodextrin, mannitol, xylitol, sorbitol, a cyclodextrin, and mixtures thereof.

8. (Original) The formulation of claim 1 wherein the lubricant is present in an amount of about 0.25% to about 2% by weight.

9. (Original) The formulation of claim 1 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, hydrogenated vegetable oils, and mixtures thereof.

10. (Original) The formulation of claim 1 wherein the hydrophilic binder is present in an amount of about 1% to about 5% by weight.

11. (Original) The formulation of claim 1 wherein the cellulose derivative is selected from the group consisting of hydroxypropylcellulose, hydroxypropyl methylcellulose, and mixtures thereof.

12. (Original) The formulation of claim 1 wherein the disintegrant is present in an amount of about 3% to about 10% by weight.

13. (Original) The formulation of claim 2 wherein the microcrystalline cellulose is present in an amount of about 5% to about 40% by weight.

14. (Original) The formulation of claim 3 wherein the wetting agent is present in an amount of 0.1% to about 5% by weight.

15. (Original) The formulation of claim 14 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, docusate sodium, ethoxylated castor oil, a polyglycolyzed glyceride, an acetylated monoglyceride, a sorbitan fatty acid ester, a poloxamer, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene, a monoglyceride and ethoxylated derivatives thereof, a diglyceride and ethoxylated derivatives thereof, and mixtures thereof.

16. (Previously presented) The formulation of claim 15 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, polysorbate 80, and a mixture thereof.

17. (Cancelled)

18. (Original) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 10 microns.

19. (Original) The formulation of claim 1 comprising:

(a) about 1% to about 4% by weight of the active compound;

(b) about 50% to about 75% by weight lactose;

(c) about 0.25% to about 2% by weight magnesium stearate;

(d) about 1% to about 5% by weight hydroxypropyl cellulose; and

(e) about 3% to about 10% by weight croscarmellose sodium.

20. (Original) The formulation of claim 18 further comprising about 5% to about 40% by weight microcrystalline cellulose.

21. (Original) The formulation of claim 18 further comprising about 0.1% to about 5% by weight sodium lauryl sulfate.

22. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 20 mg per tablet.

23. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 to about 15 mg per tablet.

24. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 mg per tablet.

25. (Original) A capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles, wherein the active compound is present in an amount of about 1 to about 20 mg per capsule.

26. (Cancelled)

27. (Cancelled)

28. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 30 microns.

29. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 25 microns.

30. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 15 microns.

31. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 10 mg per tablet.

32. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 5 mg per tablet.

33. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 2.5 mg per tablet.

34. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 20 mg per tablet.

35. (Previously presented) A method of treating sexual dysfunction in a patient in need thereof comprising administering to the patient an effective amount of a formulation or a tablet according to of any one of claims 1 through 4, 6 through 16, 18 through 25, or 28 through 30.

36. (Previously presented) The method of claim 35 wherein the sexual dysfunction is male erectile dysfunction.

37. (Cancelled)

REMARKS

Claims 1-4, 6-16, 18-25 and 28-36 are pending in the application and are at issue.

Claims 1-4, 6-16, 18-25, and 28-37 stand rejected under 35 U.S.C. §103 as being unpatentable over WO 97/03675 (WO '675) in view of WO 96/38131 (WO '131 and U.S. Patent No. 4,721,709 ('709). In view of the Declaration of Martha A. Kral (Kral Declaration) submitted concurrently with this amendment, and for the reasons set forth below, it is respectfully submitted that this rejection should be withdrawn.

In Amendment "B" filed on July 11, 2005, applicants provided a description of the present invention, and the benefits provided by the presently claimed invention. This description is reiterated below for the convenience of the examiner, and the attached Kral Declaration clearly shows surprising and unexpected results of the present invention and also supports the benefits described below with objective evidence from a comparison of the presently claimed formulations to formulations in the cited primary reference.

The present invention is directed to a pharmaceutical formulation, which exhibits unexpected and surprising results in therapeutic delivery of Compound (A) through enhanced dosage uniformity, stability, and bioavailability. As a result, the present invention achieves a rapid onset of a therapeutic effect, which has been identified as a problem involving the β-carboline (see specification, page 1, lines 16-19; page 2, line 24 through page 3; page 7, lines

21-28). The unexpected and surprising results of the present formulation are achieved because of (i) the presence of Compound (A) as a free drug comprising a particle size of less than about 40 microns *and* (ii) the presence and amounts of other important formulation ingredients, such as a water-soluble diluent, a lubricant, a hydrophilic binder, and a disintegrant. The present application specifically discloses that "the particle size of the active compound also has been found to enhance the bioavailability and handling of the present formulation" (see specification page 8, lines 14-23). The effects and importance of other formulation ingredients are also disclosed in detail, for example, at page 9, lines 24-33; and page 10, lines 16-23. Furthermore, the present invention provides a formulation having improved stability over prior formulations, in addition to improved dissolution and *in vivo* adsorption (page 12, line 32 through page 12, line 2). These advantages over compositions disclosed in WO '675 are demonstrated in the attached Kral Declaration.

Briefly, WO '675 discloses a method of treating male erectile dysfunction using Compound (A) and a tablet containing Compound (A), i.e., tablet formulations A.1., A.2., B.1., and B.2. at pages 12-15 of the specification. However, as stated by the examiner, WO '675 fails to teach or suggest use of a free drug form of Compound (A), the particle size of Compound (A), *or* the specifically claimed formulation, let alone all three features.

As stated above, the presently claimed formulations provide a stable composition that effectively

delivers the claimed compound (i.e., Compound (A)) *in vivo*. Because Compound (A) is a highly water-insoluble drug, its formulation into a pharmaceutical composition that effectively delivers the drug is not straightforward. As a result of applicants' investigation, a pharmaceutical composition that is surprisingly physically stable, and that demonstrates improved dissolution and *in vivo* absorption has been achieved.

The differences between WO '675 and the present claims are substantial. First, the presently claimed formulation contains Compound (A) as a free drug in a claimed particle size, whereas WO '675 fails to teach or suggest either of these features of Compound (A). These features, together with the other claimed formulation ingredients, provide the new and unexpected benefits achieved by the presently claimed invention described above.

In addition, the presently claimed formulations, as a whole, are substantially different from the formulations disclosed in WO '675. This is further illustrated by the Kral Declaration discussed below. The following table compares a composition disclosed in WO '675, and relied upon by the examiner, to the presently claimed compositions.

Ingredient	WO '675[1)]	Claim 1
1. Compound (A)	10% w/w	present
2. polyvinyl pyrrolidone (PVP)	30% w/w	present
3. polyethylene glycol (PEG)	10% w/w	not present
4. polysorbate 80	2% w/w	present (claim 3)
5. magnesium stearate colloidal silicon dioxide	0.5% w/w 0.5% w/w	present
6. croscarmellose sodium	5% w/w	present
7. microcrystalline cellulose	42% w/w	present (claim 2)
8. water-soluble diluent	not present	50-80% w/w

[1)] Formulation B.1. at page 13 of WO '675.

The compositions of WO '675 and claim 1 (or a claim depending therefrom) both include Compound (A), a wetting agent (e.g., polysorbate 80), a lubricant (magnesium stearate and colloidal silicon dioxide), croscarmellose sodium, and microcrystalline cellulose.

However, the compositions then greatly differ. For example,

(a) the composition of WO '675 contains PEG. Claims 1 and 6 recite a water-soluble diluent, including a polyol, which by definition does not include PEG. See the diluent examples in the specification (all of which are solids at room temperature), and see the definition of a "polyol" previously provided with Amendment "A."

(b) the composition of WO '675 contains 10% w/w PEG, which even if considered a water-soluble diluent, as stated by the examiner, is far below the 50-85% w/w recited in claim 1 for the water-soluble diluent.

(c) the composition of WO '675 contains 30% w/w PVP, whereas the present formulation contains a much lower amount of hydrophilic binder of about 1-5%

w/w. Furthermore, WO '675 fails to teach or suggest a cellulose derivative as the hydrophilic binder. Contrary to the examiner's statement, applicants did not previously argue that WO '675 does not teach PVP. As stated above, WO '675 does not teach a cellulose derivative.

In view of the above, WO '675 fails to teach the "same" pharmaceutical compositions containing the "same" active compound and excipients, as asserted by the examiner, and WO '675 fails to teach or suggest the present invention as a whole. Accordingly, it is submitted that the present invention as a whole would not have been obvious over WO '675.

The Kral Declaration is submitted to demonstrate the unexpected and surprising results of the presently claimed invention and to further demonstrate the differences between a presently claimed formulation and formulation examples disclosed in WO '675. As set forth in the Kral Declaration in paragraph 9, Example B1 of WO '675 is neither a workable nor a practicable formulation and process. Example B1 contains 10% PEG as a binder, which is known to potentially prolong tablet disintegration time. Such a thermoplastic granulation is used to prepare dosage forms that dissolve slowly, which negates advantages of the present invention, i.e., rapid dissolution for rapid onset of action and enhanced bioavailability. See Kral Declaration, paragraph 9.

Formulations of the present invention incorporating a water-soluble diluent, i.e., lactose monohydrate, together with a hydrophilic binder pro-

vided good granulation for compressibility (Kral Declaration, paragraph 16). This could not be accomplished using PEG as a water-soluble diluent, and the disadvantages of PEG in the formulation as applied to the present invention are discussed further in paragraph 9 of the Kral Declaration.

Examples A2 and B2 of WO '675 are addressed in paragraphs 10-13, 15, and 17-19 of the Kral Declaration. The Kral Declaration demonstrated that tablets prepared from Example A2 of WO '675 are extremely hard and failed to release an acceptable amount of the drug during dissolution (Kral Declaration, paragraph 13). Tablets made in accordance with Example B2 of WO '675 dissolved very quickly, but were too soft to maintain tablet integrity in further manufacturing steps (Kral Declaration, paragraph 15).

The Kral Declaration, at paragraphs 16-20, demonstrates that tablets prepared from a presently claimed formulation (a) overcome the problems associated with the tablets of WO '675 as stated above *and* (b) exhibit the unexpected and surprising benefits of tablet stability, a rapid therapeutic onset, and good bioavailability (paragraph 17). In particular, paragraph 17 of the Kral Declaration states how formulation changes employed by the present invention that were neither taught nor suggested by WO '675 produced tablets that overcame prior problems and provided unexpected and surprising results. These unexpected results are described in paragraphs 18 to 20 of the Kral Declaration with respect to tablet hardness (which helps maintain the integrity of the tablet for further

manufacturing processes) and dissolution rates wherein a present formulation releases the drug more quickly and more completely to provide a rapid onset of the therapeutic effect and enhanced bioavailability.

Moreover, in addition to the reasons set forth above and the unexpected results demonstrated in the Kral Declaration, the nonobviousness of the present invention is further demonstrated by claimed features that the examiner acknowledges are *not* disclosed or suggested in WO '675, i.e., particle size of Compound (A), percentages of ingredients, and amounts of drug in the tablet or capsule (see Office Action, page 3, lines 12-14). The examiner also made an erroneous assumption in reasoning by concluding that WO '675 teaches a free form of Compound (A) because WO '675 fails to disclose an imbedded form of Compound (A). This conclusive basis of rejection and reasoning cannot, without any support, be maintained because it is not in accordance with well-established standard of obviousness test. WO '675 is silent with respect to the form of Compound (A) in the formulation, and thus simply did not disclose this aspect of the present invention.

The secondary WO '131 and '709 references do not overcome the deficiencies of WO '675 for the reasons stated below.

WO '131 is directed to, *and limited to*, improving the bioavailability of poorly water-soluble drugs, like Compound (A), by forming a *coprecipitate dispersion*. WO '131 explains the problems associated with poorly water-soluble drugs in the free form, e.g., poor bioavailability, and teaches that solid disper-

sions of a poorly water-soluble drug may overcome these problems. WO '131 then discloses a coprecipitation technique that overcomes the problems associated with poorly water-soluble drugs in the free form and prior solid dispersions. See WO '131, pages 1-4.

Unlike the present invention, WO '131, therefore, teaches (a) the advantages of forming a coprecipitate, and (b) *avoiding* the free form of a poorly water-soluble drug, like Compound (A), in order to improve dissolution of the drug. WO '131 provides absolutely no teaching or motivation to utilize a free form of Compound (A) in a pharmaceutical formulation to achieve enhanced bioavailability and stability, but rather teaches away from using the free form of Compound (A) to achieve what has achieved by the presently claimed formulation. In fact, it is the problem encountered using a free form of a poorly water soluble drug that WO '131 addresses and attempts to solve.

Moreover, WO '131 discloses formulations that contain Compound (A) only as a coprecipitate, which again is substantially different from the presently claimed formulations. Therefore, contrary to the examiner's contention, the specific β-carboline coprecipitate compound taught in WO '131 is *different from* the presently claimed free form of Compound (A) in the claimed particle size. In addition, the examiner acknowledges at page 4 of the Office Action that WO '131 "fails to teach the claimed particle sizes," and further, WO '131 fails to suggest using the claimed particle size. Finally, the formulations disclosed in WO

'131 at pages 16-19 are substantially different from the presently claimed compositions as a whole.

The examiner contends that WO '131 "nowhere compares and teaches away from preparing a free drug formulation as opposed to the preferred co-precipitate." The examiner is referred to page 1, lines 3-8 of WO '131, which clearly states that the WO '131 invention relates to coprecipitates, and to *all* examples which utilize coprecipitates. WO '131 does not provide a comparison between a free drug form and a coprecipitate because it clearly states the disadvantages of the poorly water-soluble drug, e.g., Compound (A), and solves these problems by coprecipitation.

In view of the above, the cited references, alone or in combination, fail to provide a teaching or suggestion to modify and arrive at the presently claimed invention as a whole, and the modification would be successful in achieving unexpected and surprising results as stated in detail above. Accordingly, the present invention, as a whole, is not obvious over the cited references alone or in combination.

Seth et al. '709 also fails to cure the deficiencies of the combined teachings of WO '675 and WO '131. The '709 patent merely teaches fine particle size benzodiazepine drugs *adsorbed* onto a carrier. According to '709 patent, the critical feature of the Seth invention is directed to "the fine particle size of the adsorbed hydrophobic drug" (see column 6, lines 13-14). In addition, as stated by the examiner, the "method of Seth comprises the steps of providing dry

powder of the insoluble drug that is adsorbed onto a carrier" and "Seth teaches that the drug particles are closely associated with the carrier" (Office Action, page 4). This is in direct contrast to the presently claimed feature of a *free* particle form of Compound (A), which is *not* adsorbed onto a carrier. The '709 patent simply fails to teach or suggest a free form of the drug, but rather teaches the *necessity and criticality* of adsorbing the drug onto a carrier (see '709 patent, column 4, lines 44-52, for example).

The '709 patent also is addressed in paragraph 9 of the Kral Declaration. The declarant notes that as disclosed in the '709 patent (column 2, lines 13-17), micronized particles have the disadvantages of agglomeration, poor flow, and poor wetting. The '709 patent overcame these problems by *adsorbing* the micronized drug onto a pharmaceutical carrier. In contrast, the presently claimed invention employs micronized free drug *without* adsorbing onto a pharmaceutical carrier, which the '709 patent requires as critical to solving the problem. Moreover, the formulations provided in the '709 patent at columns 9 and 10 are substantially different from the claimed formulations as a whole, and provide no suggestions with respect to modifying the formulation to arrive at the presently claimed formulation as a whole. The '709 patent, therefore, not only fails to teach or suggest a free form of a drug, but also fails to teach or suggest any formulations or formulation modifications that would help overcome the deficiencies of WO '675 and WO

'131, taken alone or in combination, to render the present claims obvious.

Furthermore, as previously stated, the examiner misapplies applicants' incorporation of U.S. Patent No. 4,605,517 in the present specification ('517) by reference. As specifically stated in the present specification at page 8, lines 28-32, the '517 patent is incorporated by reference *merely* for the purpose of instructing persons reading the present specification how to measure particle size, and, thus, the '517 patent is not referenced for a method of preparing the present formulations. Preparation of the present formulations is illustrated in the examples of the present application, and, thus, do not rely upon the method of U.S. Patent No. 4,605,517.

In summary, for the reasons stated above, and because of the unexpected results demonstrated by the Kral Declaration, the present invention, as a whole, is neither taught nor suggested by any of the cited references, alone or in combination. Accordingly, it is respectfully submitted that the rejection under 35 U.S.C. §103 should be withdrawn.

Claims 1-4, 6-16, 18-25, and 28-36 also stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,821,975. In view of the terminal disclaimer filed concurrently with this amendment, it is submitted that this rejection has been overcome and should be withdrawn.

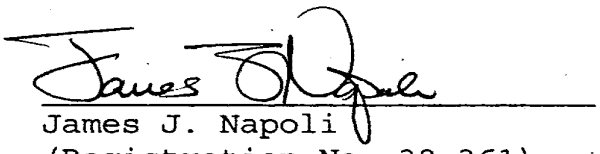
In summary, it is submitted that the present claims are in a form and scope for allowance. An early

and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

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Chicago, Illinois
December 21, 2005

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: **December 21, 2005**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE-PATENTING REJECTION OVER AN ISSUED PATENT

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

Sir:

The undersigned, having power of attorney from the assignee, Lilly ICOS LLC, has executed this document on behalf of petitioner, Lilly ICOS LLC. Petitioner is a Delaware corporation, 1209 Orange Street, Wilmington, Delaware 19801, and is the owner of 100% interest in the instant application, as shown by the assignment recorded May 8, 2002, at Reel 12877, Frame 0177. Petitioner hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which

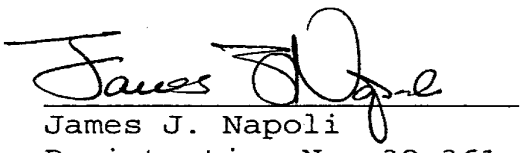
would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §154 to §156 and §173, as presently shortened by any terminal disclaimer of prior Patent No. 6,821,975. Petitioner also is the owner of 100% interest in U.S. Patent No. 6,821,975 as shown by the assignment recorded on July 20, 2002 at Reel 13114, Frame 0703. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and U.S. Patent No. 6,821,975 are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, petitioner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §154 to §156 and §173 of prior Patent No. 6,821,975, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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; further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereof.

The Commissioner is hereby authorized to credit any overpayment or charge any additional fees which may be required during the pendency of this application under 37 C.F.R. §1.16 or 37 C.F.R. §1.17 or under applicable rules (except payment of issue fees), to Deposit Account No. 13-2855. A copy of this transmittal is enclosed.



James J. Napoli
Registration No. 32,361

Dated: December 21, 2005

☒ Our firm check in the amount of $130.00 is enclosed in payment of the requisite Terminal Disclaimer fee under 37 C.F.R. §1.20(d).

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: **December 21, 2005**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

DECLARATION OF MARTHA A. KRAL UNDER 37 C.F.R. §1.132

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

Sir:

NOW COMES MARTHA A. KRAL, Declarant herein, and states as follows:

1. I am a coinventor of the invention disclosed and claimed in the above-identified patent application.

2. I am presently employed by Eli Lilly and Company, Indianapolis, IN. My present title is Research Advisor. I have been employed by Eli Lilly and Company since 1998, engaged in product development and technical support of pharmaceutical formulations.

3. Previous to my employment at Eli Lilly and Company, I was employed at Hoechst Marion Roussel Inc., and the predecessor company, Marion Merrell Dow, Inc., Kansas City, MO from 1992 to 1998, providing technical support and developing pharmaceuticals and bioproducts. Prior to transferring to Kansas City, MO, I was employed at Marion Merrell Dow, and the predecessor company Merrell Dow, Cincinnati, OH from 1989 to 1992 in pharmaceutical research.

4. I have earned a B.A. in Biology (1975), and an M.S. (1985) and a Ph.D. (1990) in Pharmaceutical Chemistry, all from the University of Kansas, Lawrence, KS.

5. Throughout my academic and professional careers, I conducted research in the pharmaceutical arts and helped develop formulations for commercial drug products. I am a member of the American Associate of Pharmaceutical Scientists (AAPS).

6. I have read and understand the Office Action dated September 21, 2005, which was issued in connection with U.S. Patent Application Serial No. 10/031,464. I also have read and understand the following references cited by the examiner in U.S.S.N. 10/031,464:

WO 97/03675 (WO '675);
WO 96/38131 (WO '131); and
Seth et al. U.S. Patent No. 4,721,709 ('709).

7. Pending claims 1-4, 6-16, 18-25, and 28-36 of U.S.S.N. 10/031,464 were rejected as being obvious over a combination of the WO '675, WO '131, and '709 references because

> "[D]uang [sic] teaches the claimed beta-carboline compounds and compositions containing the compounds, as also acknowledged by applicants on page 2 of the instant application. Daung [sic] specifically discloses teaches [sic] instant preferred compound (instant specification, page 3, lines 28-30) for treating conditions where inhibition of PDE5 is beneficial (see page 3, lines 24-25, lines 30-32 and is also referred to as compound A). On page 12, lines 11-12, Daung [sic] teaches that the compounds a [sic] and B are prepared as different dosage forms and in particular, Table B shows a tablet prepared by wet granulation, where in the tablet composition contains beta-carboline drug as active agent and other excipients such as polyvinylpyrrolidone, PEG, Polysorbate 80, magnesium stearate, cross-caramellose [sic] sodium, and microcrystalline cellulose, which read on the instant claimed binder, diluent, wetting agent, lubricant and disintegrant respectively. Instant dependent claims specifically recite the excipients of Table B of Daung [sic]. With respect to the percentages of active ingredients and the excipients claimed, the total weight of the composition of tablet in Table B is 500 mg. A calculation of the proportion of each ingredient in Table 2 reads on the instant claimed percentages. With respect to the claimed 'free drug', Daung [sic] does not teach an intimately embedded drug in a polymeric co-precipitate and hence meets the definition of 'free drug' (instant page 5, lines 24-27). Instead, Daung [sic] only teaches direct compression or wet granulation followed by compression to prepare the tablets (pages 12-14)." (Office Action of September 21, 2005, pages 2 and 3).

Various dependent claims are rejected based on a contention that the claimed percentages of diluents and

particle sizes are optimizations within the "scope of a skilled artisan."

8. Based on my training and experience, the pending claims would not have been obvious to a person of ordinary skill over a combination of WO '675, WO '131, and the '709 patent. The claimed invention is directed to pharmaceutical formulations, which exhibit unexpected and surprising results in the therapeutic delivery of Compound A through enhanced bioavailability. Compound A is identified at page 7, lines 21-28 of the specification. As a result, the claimed formulations achieve a rapid onset of the therapeutic effect, which has been identified as a problem involving the beta-carboline compounds, as well as providing tablets with uniform potency and desirable stability.

9. We prepared tablets and performed tests to assess two of the examples (A2 and B2) disclosed in WO '675 and to compare those examples to the claimed formulations. Example B1 of WO '675 utilizes a nonconventional manufacturing process that includes granulation of the active ingredient, drying, and extrusion at elevated temperatures and pressures. The excipients taught in the WO '675 B1 example include 10% PEG as a binder, which at that level is known to potentially prolong the disintegration time of tablets. When excipients in the B1 example are manufactured by the described process, a thermoplastic granulation is produced. This type of process is typically used to prepare dosage forms that are meant to dissolve slowly, such as lozenges. These tablet properties would not solve the problem that our invention overcomes,

specifically, rapid dissolution to achieve rapid onset of action and enhanced bioavailability. Thus, the Daugan B1 example teaches neither a workable nor a practicable formulation and process.

10. Example A2, a direct compression formulation, and Example B2, a wet granulation formulation, of WO '675 were manufactured as 10 mg tablets, rather than 50 mg tablets, because this dosage is one of the preferred tablet strengths. The formulations of these examples were manufactured at a laboratory scale of 15,000 to 18,000 tablets, and were adjusted for the decrease in the percent loading of Compound A by an equal increase in the percent loading of one excipient, i.e., microcrystalline cellulose in Example A2 and lactose in Example B2. The same lot of Compound A, which contained a small particle size as recited in claim 1 of the application, was used in all formulations discussed herein. Based on my training and experience, the 50 mg tablets in Examples A2 and B2 disclosed in WO '675 would be expected to exhibit similar tablet properties as the 10 mg tablets manufactured because the adjustment of the formulas is slight. These unit formulas are provided in Tables 1 and 2 below.

11. Table 1 provides the unit formulas for the 50 mg tablets disclosed in Example A2 of WO '675 and the 10 mg tablets manufactured by direct compression.

Table 1. Unit Formula Comparison of WO '675 Example A2				
	WO '675 Example A2 (50 mg)		Applicant Example A2 (10 mg)	
Ingredient	**mg/tablet**	**% w/w of core tablet**	**mg/tablet**	**% w/w of core tablet**
Active Ingredient (Compound A)	50.0	25.00	10.0	5.00
Colloidal Silicon Dioxide	0.5	0.25	0.5	0.25
Crospovidone	8.0	4.00	8.0	4.00
Sodium Lauryl Sulfate	1.0	0.50	1.0	0.50
Magnesium Stearate	1.0	0.50	1.0	0.50
Microcrystalline Cellulose	139.5	69.75	179.5	89.75
Total core tablet	200.0	100.00	200.0	100.00

12. Table 2 provides the unit formulas for the 50 mg tablets disclosed in Example B2 of WO '675 and the 10 mg tablets manufactured by wet granulation.

Table 2. Unit Formula Comparison of WO '675 Example B2				
	WO '675 Example B2 (50 mg)		Applicant Example B2 (10 mg)	
Ingredient	**mg/tablet**	**% w/w of core tablet**	**mg/tablet**	**% w/w of core tablet**
Active Ingredient (Compound A)	50.0	16.67	10.0	4.00
Polysorbate 80	3.0	1.00	2.5	1.00
Lactose	178.0	59.33	180.0	72.00
Starch	45.0	15.00	37.5	15.00
Pregelatinized Starch	22.5	7.50	18.75	7.50
Magnesium Stearate	1.5	0.50	1.25	0.5
Total core tablet	300.0	100.00	250.00	100.00

13. The tablets manufactured by direct compression based on Example A2 of WO '675 were extremely hard (about 23 kp) and failed to release a sufficient amount of the drug during dissolution testing to be acceptable. In other words, the dissolution of the

free drug particles of Compound A from the tablet is incomplete, indicating that the formulation is inherently the cause of the low dissolution.

14. Seth (WO '709) discloses in Column 1, lines 66 - 68 and Column 2, lines 1 - 20 that a frequently used method to overcome the slow rate of dissolution of poorly soluble, hydrophobic drugs is to finely grind or 'micronise' drug substances so as to reduce their particle size. A major disadvantage of such grinding methods is the resulting tendency of the milled particles to agglomerate and the formation of an electrostatic charge on their surfaces which leads to poor flow and wetting of the particles. Seth taught that these problems could be overcome by adsorbing a hydrophobic, poorly soluble drug to a pharmaceutical carrier (Column 4, lines 44 - 48). However, Seth did not teach nor suggest how to utilize micronised free drug to improve bioavailability without adsorbing the drug to the carrier. Surprisingly, our invention was able to use micronised free drug without adsorbing the drug on to a carrier to achieve uniform potency, rapid absorption, and improved bioavailability.

15. The tablets manufactured by wet granulation based on Example B2 of WO '675 dissolved very quickly. However, these tablets were so soft (about 2 kp) that they were not sufficiently robust for a further manufacturing step, such as film coating, without significant breakage or erosion.

16. To solve the above problems of unacceptably low tablet dissolution and insufficient tablet hardness, the formulations of the present invention were developed based on many experiments to find the

proper combination and quantities of excipients to provide physically robust tablets that also released the drug quickly and completely. The removal of starch to obtain acceptable tablets was not taught by Daugan, and several additional changes to the formulation, as discussed below, were required to produce tablets with the appropriate properties. To illustrate the advantages of the presently claimed formulation, the 10 mg formula of Example 1 of the present specification is provided in Table 3.

Table 3. Unit Formula for 10 mg Tablet (Example 1)

Ingredient	mg/tablet	% w/w of core tablet
Granulation		
Active Ingredient (Compound A)	10.0	4.00
Lactose Monohydrate	153.8	61.52
Spray Dried Lactose Monohydrate	25.0	10.00
Hydroxypropyl Cellulose	4.0	1.60
Croscarmellose Sodium	9.0	3.60
Hydroxypropyl Cellulose (EF)	1.75	0.70
Sodium Lauryl Sulfate	0.7	0.28
Outside Powders		
Microcrystalline Cellulose	37.5	15.00
Croscarmellose Sodium	7.0	2.80
Magnesium Stearate	1.25	0.50
Total core tablet	250.0	100.00

The 10 mg tablets were manufactured at a laboratory scale (18,000 tablets). The use of a water-soluble diluent, i.e., lactose monohydrate, with a hydrophilic cellulosic binder (hydroxypropylcellulose), provided a good granulation. The addition of spray dried lactose monohydrate enhanced the compressibility of the final granulation, as did the outside powder addition of microcrystalline cellulose, resulting in tablets that were sufficiently hard to withstand the coating process, packaging, and shipping.

17. The tablets prepared according to Table 3 disintegrated and dissolved rapidly to meet the therapeutic need for rapid onset of Compound A. WO '675 fails to teach or suggest that modifying the level of microcrystalline cellulose, or removing the relatively small quantities of water insoluble starch (22.5% of the tablet) and using only water soluble lactose in the granulation would significantly improve tablet hardness. Surprisingly, the present formulation solved the above-mentioned problems and produced tablets that not only provide a rapid therapeutic onset, but also are stable and achieve good bioavailability.

18. Table 4 summarizes the compressibility of the three granulation compositions provided in Tables 1 to 3, as measured by tablet hardness in kiloponds (kp), at various tablet press compression forces.

Table 4. Tablet Hardness Values as a Function of Compression Force

Compression Force (kg)	Hardness (kp)		
	WO '675 A2 (10 mg)	WO '675 B2 (10 mg)	Example 1 (10 mg)
1100	22.9	1.4	6.6
1600	23.5	2.1	9.6
1800	23.2	2.3	9.0
2100	24.1	2.4	9.3

The tablets from Example A2 of WO '675 were very hard, and the hardness did not vary across an increase of 1000 kg of compression force. This indicates that the formulation is inherently the cause of the hard tablets. Similarly, the hardness of Example B2 of WO '675 varied slightly and the consistent low hardness values indicate that this is caused by the tablet formulation. The tablets of the present formulation (Example 1) demonstrate an increased hardness as a

function of compression force, and that the tablets are sufficiently robust to be further processed.

19. Table 5 summarizes the dissolution release time profiles of Compound A from the three tablet compositions described in Tables 1 to 3.

Table 5. Average Tablet Dissolution Results (n=6)

Time (minutes)	% Compound A Released		
	WO '675 A2 (10 mg)	WO '675 B2 (10 mg)	Example 1 (10 mg)
0	0	0	0
5	43	57	44
10	58	97	81
20	70	99	95
30	77	99	96
45	82	99	97

The dissolution data for the very hard tablets from Example A2 of WO '675 (Table 4) demonstrate that an incomplete release of the drug (82%) was achieved after 45 minutes. While the release of the drug from Example B2 of WO '675 was complete, the tablets were unacceptably soft and would not maintain integrity during further manufacturing processes. The tablets of the present formulation (Example 1) released the drug more quickly and more completely than Example A2 of WO '675 and had sufficient hardness to be coated, packaged, and shipped.

20. In summary, the presently claimed formulations as a whole solve the problems not taught by Daugan, Seth, and Butler, alone or in combination. Through these innovative formulations, the present invention provides unexpected and surprising results in the therapeutic delivery of Compound A by providing a rapid onset of the therapeutic effect and enhanced bioavailability, as well as providing tablets with uniform potency and desirable stability.

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

Martha A. Kral

Martha A. Kral

Dated: 15 Dec 2005

ITW 1615

AMENDMENT TRANSMITTAL LETTER

Docket No. 29342/36230A

Application No.	Filing Date	Examiner	Art Unit
10/031,464-Conf. #6930	April 29, 2002	L. S. Channavajjala	1615

Applicant(s): Peter L. Oren et al.

Invention: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims	56	- 88 =		x	
Independent Claims	1	- 3 =		x	
Multiple Dependent Claims (check if applicable)	☐				
Other fee (please specify): Terminal Disclaimer fee					
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					130.00

☒ Large Entity ☐ Small Entity

☒ No additional fee is required for this amendment.

☐ Please charge Deposit Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

☒ A check in the amount of $ 130.00 to cover the filing fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge and credit Deposit Account No. 13-2855 as described below. A duplicate copy of this sheet is enclosed.

☒ Credit any overpayment.

☒ Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.

James J. Napoli

Dated: December 21, 2005

James J. Napoli
Attorney Reg. No.: 32,361

MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: December 21, 2005 Signature: _____ (James J. Napoli)

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number
10/031464

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	26 minus 20=	* 6
INDEPENDENT CLAIMS	1 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	88
X$ 9=		OR	X$18=	108
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A 9/27/04

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 88	Minus	** 26	* 62
Independent	* 2	Minus	*** 3	* —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☑

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	1116
X42=		OR	X84=	—
+140=		OR	+280=	290
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	1406

AMENDMENT B 11/1/05

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 78	Minus	** 88	=
Independent	* 11	Minus	*** 2	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C 12/27/05

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 31	Minus	** 78	=
Independent	* 1	Minus	*** 1	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
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.

FORM PTO-875 (Rev 8/01)

Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/031,464	OREN ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 27 DEC 2005	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

U.S. Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

4743 7590 04/06/2006

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- 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 *27 December 2005*.

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) *1-4,6-16,18-25 and 28-36* 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) *1-4,6-16,18-25 and 28-36* 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-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of response, declaration and terminal disclaimer all dated 12-27-05 is acknowledged.

Claims 1-4, 6-16,18-25 and 28-36 are pending in the instant application.

Response to Arguments

Applicants' arguments presented 12-27-05 regarding the following prior art rejection of record have been persuasive and hence the rejection has been withdrawn:

1. Claims 1-4, 6-16, 18-25 and 28-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03675 (Daung) in view of WO 96/38131 (Butler) and US 4,721,709 to Seth et al (Seth).

In response to the terminal disclaimer filed on 12-27-05, the following rejection has been withdrawn:

2. Claims 1-4, 6-16, 18-25 and 28-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U. S. Patent No. 6,821,975.

The following is a new rejection:

1. Claims 1-4, 6-16, 18-25 and 28-37 are directed to an invention not patentably distinct from claims 1-11 of commonly assigned US 6,821,975. Specifically, instant claimed composition containing a free drug, beta-carboline together with excipients and the method of treating sexual dysfunction using the composition comprising particulate form of the drug, is also claimed in the above patent applications. The patented claims

of '975 recite compositions comprising the same free drug of instant compound, including particle sizes and broadly recite carriers or excipients, as in instant claims. While the patent fails to list the specific diluents and other excipients of the instant claims, choosing appropriate solvents, diluents, and other art recognized pharmaceutical excipients with an expectation to prepare a desired dosage form would have been obvious for one of an ordinary skill in the art.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US 6,943,166, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

2. Claims 1-4, 6-16, 18-25 and 28-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,943,166 ('166) in view of US 6,821,975 ('975).

'166 claims a method of treating sexual dysfunction in a patient by administering a unit dose of a composition containing a compound, which is the same as the beta-carboline claimed in the instant invention. '166 claims unit dose in the form of a tablet, capsule, gel cap etc. '166 does not claim a pharmaceutical composition, free drug comprising particles, and the excipients of the instant claims.

'975 claim a composition and method similar to that of the instant claims. In particular, the compound claimed in '975 is the same as that of the free drug comprising particles, claimed in the instant invention. '975 broadly teach excipients such as diluents, carrier and diluents. Thus, the method claimed by '166 is the same as that of instant claims. All three sets of the claims employ the same compound as the active agent. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use the compound of '166 to prepare a pharmaceutical composition in the form of tablets or capsules (such as those claimed in the instant), wherein the composition employs the active compound as it is or as a free drug comprising particles of the claimed sizes. While the instant claims recite specific excipients, '975 broadly suggests employing excipients and accordingly employing suitable excipients, diluents or carriers so as to prepare tablets or capsule that are effective in treating sexual dysfunction would have been within the scope of a skilled artisan. However, choosing appropriate solvents, diluents, and other art recognized

pharmaceutical excipients with an expectation to prepare a desired dosage form would have been obvious for one of an ordinary skill in the art.

3. Claims 1-4, 6-16, 18-25 and 28-37 are directed to an invention not patentably distinct from claims 1-12 of commonly assigned US 6,943,166 in view of US 6,821,975. Specifically, instant claims composition containing a free drug, beta-carboline, together with excipients and the method of treating sexual dysfunction using the claimed composition comprising particulate form of the drug. US patent '166 claims a method of treating the same condition as that of the instant, employing the same compound. The patented claims of '975 recite free form drug, particle sizes and broadly recite carriers or excipients, similar to the instant claims. While the patent fails to list the specific diluents and other excipients of the instant claims, choosing an appropriate solvents, diluents, and other art recognized pharmaceutical excipients with an expectation to prepare a desired dosage form would have been obvious for one of an ordinary skill in the art.

The U.S. Patent and Trademark Office normally will not institute interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US 6,821,975, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were

commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Claim Rejections - 35 USC § 103

Claims 1-4, 6-16, 18-25 and 28-37 are rejected under 35 U.S.C. 103(a) as being obvious over Us 6,943,166.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer

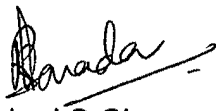
in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

'166 teach pharmaceutical compositions comprising beta-carboline compound having the same formula as that of the instant claims and for treating the same method i.e., erectile dysfunction. '166 teach 1-20 mg of active compound (also claimed in the instant) in an oral dosage form such as tablets or capsules (col. 3, lines 1-5 and 55-59), wherein the drug is present as a "free drug" i.e., solid particles of drug not intimately embedded in a polymeric co-precipitate (col. 4, lines 1-3, lines 61-64). '166 further teaches excipients and methods of preparing the dosage forms such as those claimed as well as described in the instant application (examples in col. 10-11). Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare a composition comprising the claimed compound as a free drug, having particle size of 90% particles being less than 40 microns, and preparing tablets or capsule with the excipients because '166 teaches that the dosage forms with a free drug is preferred and '166 also teaches a method of treating the same conditions as claimed. Accordingly, a skilled artisan would have been able to provide an effective treatment for sexual dysfunction with a composition containing free drug particles.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. 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).



Lakshmi S Channavajjala
Examiner
Art Unit 1615
March 31, 2006

Notice of References Cited	Application/Control No. 10/031,464	Applicant(s)/Patent Under Reexamination OREN ET AL.	
	Examiner Lakshmi S. Channavajjala	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,943,166	09-2005	Pullman et al.	514/250
	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
10/031,464	OREN ET AL.
Examiner	**Art Unit**
Lakshmi S. Channavajjala	1615

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	3/31/06
	1	✓
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/031,464	OREN ET AL.
Examiner	**Art Unit**
Lakshmi S. Channavajjala	1615

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
discussed prior art rejection of record and 1.132 declaration submitted in response to the rejection with Jonny Railey, QAS. Mr. Railey suggested ~~the~~ ~~patents~~ to withdraw art rejection	3/30/2006	LC

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

4743 7590 06/29/2006

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Interview Summary	Application No.	Applicant(s)	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) *James Napoli*. (3)_____.

(2) *Lakshmi Channavajjala*. (4)_____.

Date of Interview: *27 June 2006*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: *rejections of record*.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Discussed the double patenting rejections of record. In response to attorney's query regarding the terminal disciaimer filed on 12-27-05 over US Patent No. 6821975, examiner informed that the terminal disclaimer has been approved and the rejection is no longer applicable. Discussed the possibility of filing a terminal disclaimer to overcome the double patenting rejection over US patent No. 6943166 in view of 6821975 and also filing common ownership statement in response to the rejection under 35 USC 103(a) over 6943166. .

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: **August 7, 2006**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

RESPONSE TO OFFICE ACTION

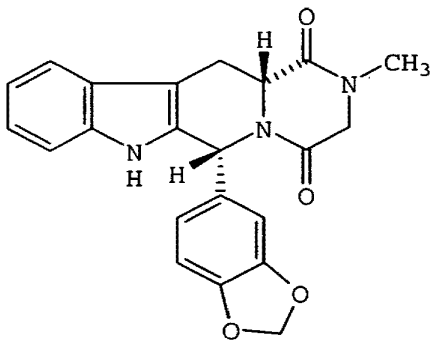
Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a response to the Office Action of April 6, 2006. Reconsideration and allowance of the application are respectfully requested.

THE CLAIMS ON FILE:

1. (Previously presented) A pharmaceutical formulation comprising an active compound having the structural formula



wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles have a particle size of less than about 40 microns; about 50% to about 85%, by weight, of a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

2. (Original) The formulation of claim 1 further comprising microcrystalline cellulose.

3. (Original) The formulation of claim 1 further comprising a wetting agent.

4. (Original) The formulation of claim 1 wherein the active compound is present in an amount of about 0.5% to about 10% by weight.

5. (Cancelled)

6. (Original) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of a sugar, a polysaccharide, a polyol, a cyclodextrin, and mixtures thereof.

7. (Previously presented) The formulation of claim 1 wherein the water-soluble diluent is selected from the group consisting of lactose, sucrose, dextrose, a dextrate, a maltodextrin, mannitol, xylitol, sorbitol, a cyclodextrin, and mixtures thereof.

8. (Original) The formulation of claim 1 wherein the lubricant is present in an amount of about 0.25% to about 2% by weight.

9. (Original) The formulation of claim 1 wherein the lubricant is selected from the group consisting of talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, calcium silicate, a starch, mineral oil, a wax, glyceryl behenate, a polyethylene glycol, sodium benzoate, sodium acetate, sodium stearyl fumarate, hydrogenated vegetable oils, and mixtures thereof.

10. (Original) The formulation of claim 1 wherein the hydrophilic binder is present in an amount of about 1% to about 5% by weight.

11. (Original) The formulation of claim 1 wherein the cellulose derivative is selected from the group consisting of hydroxypropylcellulose, hydroxypropyl methylcellulose, and mixtures thereof.

12. (Original) The formulation of claim 1 wherein the disintegrant is present in an amount of about 3% to about 10% by weight.

13. (Original) The formulation of claim 2 wherein the microcrystalline cellulose is present in an amount of about 5% to about 40% by weight.

14. (Original) The formulation of claim 3 wherein the wetting agent is present in an amount of 0.1% to about 5% by weight.

15. (Original) The formulation of claim 14 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, docusate sodium, ethoxylated castor oil, a polyglycolyzed glyceride, an acetylated monoglyceride, a sorbitan fatty acid ester, a poloxamer, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene, a monoglyceride and ethoxylated derivatives thereof, a diglyceride and ethoxylated derivatives thereof, and mixtures thereof.

16. (Previously presented) The formulation of claim 15 wherein the wetting agent is selected from the group consisting of sodium lauryl sulfate, polysorbate 80, and a mixture thereof.

17. (Cancelled)

18. (Original) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 10 microns.

19. (Original) The formulation of claim 1 comprising:

(a) about 1% to about 4% by weight of the active compound;

(b) about 50% to about 75% by weight lactose;

(c) about 0.25% to about 2% by weight magnesium stearate;

(d) about 1% to about 5% by weight hydroxypropyl cellulose; and

(e) about 3% to about 10% by weight croscarmellose sodium.

20. (Original) The formulation of claim 18 further comprising about 5% to about 40% by weight microcrystalline cellulose.

21. (Original) The formulation of claim 18 further comprising about 0.1% to about 5% by weight sodium lauryl sulfate.

22. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 20 mg per tablet.

23. (Original) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 to about 15 mg per tablet.

24. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 5 mg per tablet.

25. (Original) A capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles, wherein the active compound is present in an amount of about 1 to about 20 mg per capsule.

26. (Cancelled)

27. (Cancelled)

28. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 30 microns.

29. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 25 microns.

30. (Previously presented) The formulation of claim 1 wherein the active compound is provided as particles of a free drug wherein at least 90% of the particles have a particle size less than about 15 microns.

31. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 10 mg per tablet.

32. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 1 to about 5 mg per tablet.

33. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 2.5 mg per tablet.

34. (Previously presented) A tablet comprising the formulation of claim 1 wherein the active compound is present in an amount of about 20 mg per tablet.

35. (Previously presented) A method of treating sexual dysfunction in a patient in need thereof comprising administering to the patient an effective amount of a formulation or a tablet according to of any one of claims 1 through 4, 6 through 16, 18 through 25, or 28 through 30.

36. (Previously presented) The method of claim 35 wherein the sexual dysfunction is male erectile dysfunction.

37. (Cancelled)

REMARKS

Claims 1-4, 6-16, 18-25 and 28-36 are pending in the application and are at issue.

The courteous telephonic interview granted by Examiner Channavajjala to applicants' undersigned attorney on June 27, 2006 is hereby acknowledged with appreciation. During the interview, the outstanding Office Action was discussed in detail, most notably to clarify the rejections and to discuss responses to the rejections.

Claims 1-4, 6-16, 18-25, and 28-37 stand rejected based on the contention that the present claims are not patentably distinct from claims 1-11 of U.S. Patent No. 6,821,975 ('975). As discussed during the telephonic interview, a terminal disclaimer directed to the '975 patent was filed on December 27, 2005. The examiner acknowledged the filing of this terminal disclaimer in page 2 of the Office Action, at paragraph 2 under Response to Arguments.

During the telephonic interview, the examiner agreed that this rejection was addressed in the response of December 27, 2005 and that the previously-filed terminal disclaimer overcomes the present rejection. In summary, as agreed to by the examiner, this rejection was overcome previously and will be withdrawn.

Claims 1-4, 6-16, 18-25, and 28-37 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-12 of U.S. Patent No. 6,943,166 ('166) in view of the '975 patent. In view of the terminal disclaimer directed to

the '166 patent filed concurrently with this response, and in view of the previously filed terminal disclaimer directed to the '975 patent, it is submitted that this rejection has been overcome and should be withdrawn.

Claims 1-4, 6-16, 18-25, and 28-37 also stand rejected as being patentably indistinct from claims 1-12 of the '166 patent in view of the '975 patent under 35 U.S.C. §103(a). The Office Action states that this rejection can be overcome by showing that the present application, the '166 patent, and the '975 patent were commonly owned at the time of invention. During the telephonic interview, the examiner stated that such a showing would overcome this rejection.

Therefore, applicants state that the present application, the '166 patent, and the '975 patent were, at the time of invention of the present application, owned by, or subject to an obligation of assignment, to Lilly ICOS LLC. See MPEP §706.02(l)(1) and §706.02(l)(2). To further show that the inventions of the present application and the '166 and '975 patents were commonly owned, or subject to an obligation of assignment, at the time of invention, applicants provide the following assignment information.

Serial No.	Assignment Recordal	Provisional Application
10/031,464 (present application)	Reel 12877, Frame 177 May 8, 2002	60/146,924 filed August 3, 1999
U.S. Patent No. 6,821,975	Reel 13114, Frame 703 July 20, 2002	60/147,048 filed August 3, 1999
U.S. Patent No. 6,943,166	Reel 12740, Frame 679 March 25, 2002	60/132,036 filed April 30, 1999

The three applications are commonly owned by Lilly ICOS LLC.

In summary, it is submitted that the obviousness rejection of claims 1-4, 6-16, 18-25, and 28-37 under 35 U.S.C. §103(a) should be withdrawn because the cited '166 and '975 references are disqualified as prior art under 35 U.S.C. §103(c).

Claims 1-4, 6-16, 18-25, and 28-37 also stand rejected under 35 U.S.C. §103(a) as being unpatentable over the '166 patent. Applicants traverse this rejection.

As discussed in the prior rejection, the '166 patent is disqualified as prior art under 35 U.S.C. §103 because the present application and the '166 patent were, at the time of invention of the present application, owned by, or subject to an obligation of assignment, to Lilly ICOS LLC. Assignment information for the present application and the '166 patent are provided above.

In summary, it is submitted that the rejection of claims 1-4, 6-16, 18-25, and 28-37 over the '166 patent under 35 U.S.C. §103(a) should be withdrawn because the cited '166 reference is disqualified as prior art under 35 U.S.C. §103(c).

It is submitted that the present claims are in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
August 7, 2006

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

PETER L. OREN ET AL.

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: **August 7, 2006**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE-PATENTING REJECTION OVER AN ISSUED PATENT

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

Sir:

The undersigned, having power of attorney from the assignee, Lilly ICOS LLC, has executed this document on behalf of petitioner, Lilly ICOS LLC. Petitioner is a Delaware corporation, 1209 Orange Street, Wilmington, Delaware 19801, and is the owner of 100% interest in the instant application, as shown by the assignment recorded May 8, 2002, at Reel 12877, Frame 0177. Petitioner hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which

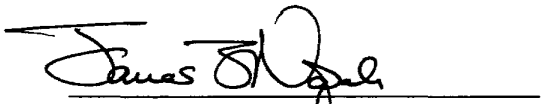
would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §154 to §156 and §173, as presently shortened by any terminal disclaimer of prior Patent No. 6,943,166. Petitioner also is the owner of 100% interest in U.S. Patent No. 6,943,166 as shown by the assignment recorded on March 25, 2002 at Reel 12740, Frame 0679. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and U.S. Patent No. 6,943,166 are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, petitioner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §154 to §156 and §173 of prior Patent No. 6,943,166, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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; further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereof.

The Commissioner is hereby authorized to credit any overpayment or charge any additional fees which may be required during the pendency of this application under 37 C.F.R. §1.16 or 37 C.F.R. §1.17 or under applicable rules (except payment of issue fees), to Deposit Account No. 13-2855. A copy of this transmittal is enclosed.



James J. Napoli
Registration No. 32,361

Dated: August 7, 2006

☒ Our firm check in the amount of $130.00 is enclosed in payment of the requisite Terminal Disclaimer fee under 37 C.F.R. §1.20(d).

TFW

#1615

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/031,464-Conf. #6930
Filing Date	April 29, 2002
First Named Inventor	Peter L. Oren
Art Unit	1615
Examiner Name	L. S. Channavajjala
Total Number of Pages in This Submission	
Attorney Docket Number	29342/36230A

ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [x] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [x] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MARSHALL, GERSTEIN & BORUN		
Signature	James J. Napoli		
Printed name	James J. Napoli		
Date	August 7, 2006	Reg. No.	32,361

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: August 7, 2006 Signature: James J. Napoli (James J. Napoli)

PTO/SB/17 (12-04v2)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person are required to respond to a collection of information unless it displays a valid OMB control number.

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 250.00

Complete if Known	
Application Number	10/031,464-Conf. #6930
Filing Date	April 29, 2002
First Named Inventor	Peter L. Oren
Examiner Name	L. S. Channavajjala
Art Unit	1615
Attorney Docket No.	29342/36230A

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 13-2855 Deposit Account Name: MARSHALL, GERSTEIN & BORUN

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fees Paid ($)**
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	**Fee ($)**	**Small Entity Fee ($)**
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	- =	_____	x _____	=	_____

Multiple Dependent Claims

Fee ($)	**Fee Paid ($)**
_____	_____

Indep. Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	- =	_____	x _____	=	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), 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).

Total Sheets		**Extra Sheets**		**Number of each additional 50 or fraction thereof**	**Fee ($)**		**Fee Paid ($)**
_____	- 100 =	_____	/50	_____ (round up to a whole number)	x _____	=	_____

4. OTHER FEE(S)

	Fees Paid ($)
Terminal Disclaimer--$130 fee	130.00
Other (e.g., late filing surcharge): 1251 Extension for response within first month	120.00

SUBMITTED BY

Signature	James J. Napoli	Registration No. (Attorney/Agent)	32,361	Telephone	(312) 474-6300
Name (Print/Type)	James J. Napoli			Date	August 7, 2006

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: August 7, 2006 Signature: James J. Napoli (James J. Napoli)

(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Peter L. Oren et al.
Ser. No.:	10/031,464
Filed:	April 29, 2002
For:	β-CARBOLINE PHARMACEUTICAL COMPOSITIONS
Art Unit:	1615
Examiner:	L. S. Channavajjala

CERTIFICATE OF SERVICE

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: August 7, 2006

James J. Napoli
Registration No. 32,361

PETITION FOR EXTENSION OF TIME

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

Sir:

This is a petition for an extension of time under 37 C.F.R. § 1.136 for the number of months checked below:

EXTENSION	FEE FOR LARGE ENTITY		FEE FOR SMALL ENTITY	
One Month	X	$ 120.00		$ 60.00
Two Months		$ 450.00		$ 225.00
Three Months		$ 1,020.00		$ 510.00
Four Months		$ 1,590.00		$ 795.00
Five Months		$ 2,160.00		$ 1,080.00

If an additional extension of time is required, please consider this a petition therefor.

08/10/2006 MBIZUNES 00000052 10031464
01 FC:1251 120.00 OP

Method of Payment of Fees

[x]	Enclosed is a check in the amount of:	$ 120.00
[ ]	Charge Deposit Account No. 13-2855 in the amount of: A copy of this transmittal is enclosed.	$

Deposit Account and Refund Authorization

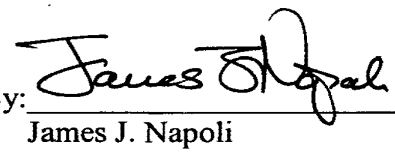
The Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees which may be required during the pendency of this application under 37 C.F.R. § 1.16 and § 1.17 to Deposit Account No. 13-2855. A copy of this transmittal is enclosed.

Please refund any overpayment to Marshall, Gerstein & Borun LLP at the address below.

Dated: August 7, 2006

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By: 

James J. Napoli
Registration No.: 32,361
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant

Barbara Campbell
National Stage Processing
(703) 305-3331

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number
10/031464

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	26 minus 20=	* 6
INDEPENDENT CLAIMS	1 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	82
X$ 9=		OR	X$18=	108
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 32	Minus	** 20	=
Independent	* 1	Minus	*** 1	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
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.

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=> d his full

     (FILE 'HOME' ENTERED AT 16:09:16 ON 23 OCT 2006)

     FILE 'REGISTRY' ENTERED AT 16:09:30 ON 23 OCT 2006
                E IFOSFAMIDE/CN
L1            1 SEA ABB=ON  PLU=ON  IFOSFAMIDE/CN
                D L1
                E TADALAFIL/CN
L2            1 SEA ABB=ON  PLU=ON  TADALAFIL/CN
                D L2

     FILE 'REGISTRY' ENTERED AT 16:11:09 ON 23 OCT 2006
                SET TERMSET E#
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                SET TERMSET LOGIN

     FILE 'CAPLUS' ENTERED AT 16:11:14 ON 23 OCT 2006
L4          330 SEA ABB=ON  PLU=ON  L3
                SET NOTICE 1000 SEARCH
L5           17 SEA ABB=ON  PLU=ON  L4 AND (PARTICLE OR PARTICULATE OR
                MICROPARTICLE OR MICRONIZ? )
                SET NOTICE LOGIN SEARCH
L6            1 SEA ABB=ON  PLU=ON  L4 (5A) (PARTICLE OR PARTICULATE OR
                MICROPARTICLE OR MICRONIZ? )
L7            2 SEA ABB=ON  PLU=ON  L4 (P) (PARTICLE OR PARTICULATE OR
                MICROPARTICLE OR MICRONIZ? )
                D L7 IBIB KWIC 1-
L8           11 SEA ABB=ON  PLU=ON  L4 AND COMPOSITION (P) (PARTICLE OR
                PARTICULATE OR MICROPARTICLE OR MICRONIZ? )
                D L8 IBIB KWIC 1-
L9            6 SEA ABB=ON  PLU=ON  L5 NOT L8
                D L9 IBIB KWIC 1-
L10           3 SEA ABB=ON  PLU=ON  TADALAFIL (P) (PARTICLE OR MICRONIZ? OR
                MICROPARTIC?)
                D L10 IBIB KWIC 1-
                D HSI FULL
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lc

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/031,464	OREN ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 8/10/06	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
vbh (6,943,166)

U.S. Patent and Trademark Office

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 10/26/2006

FPATTERS SALE #00000001 Mailroom Dt: 10/25/2006 132855 10031464
01 FC:1814 130.00 DA

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Friday, October 27, 2006

Hide?	Set Name	Query	Hit Count
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☐	L11	6841167.pn.	1
☐	L4	(beta-carboline and particle and free adj drug).clm.	0
☐	L3	(beta-carboline and particle and free adj drug and diluent and lubricant and cellulose and povidone and crospovidone and croscaramellose and binder).clm.	0
☐	L2	(beta-carboline and particle and free adj drug and diluent and lubricant and celilose and povidone and crospovidone and croscaramellose and binder).clm.	0
☐	L1	b-carboline	44

END OF SEARCH HISTORY

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

04743 7590 11/03/2006

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/03/2006

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

TITLE OF INVENTION: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$0	$0	$1400	02/05/2007

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 SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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
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)

04743 7590 11/03/2006

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

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.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

TITLE OF INVENTION: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$0	$0	$1400	02/05/2007

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHANNAVAJJALA, LAKSHMI SARADA	1615	424-464000

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 credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

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.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

04743 7590 11/03/2006

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/03/2006

Determination of Patent Term Extension under 35 U.S.C. 154 (b)
(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 0 day(s). Any patent to issue from the above-identified application will include an indication of the 0 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension 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.

Notice of Allowability	Application No.	Applicant(s)	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- 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 *8-10-06*.

2. ☒ The allowed claim(s) is/are *1-4,6-16,18-25 and 28-36*.

3. ☐ 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 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.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ 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. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *10-25-06* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

LAKSHMI S. CHANNAVAJJALA
PRIMARY EXAMINER
AU 1615

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with James Napoli on 10-25-06.

The application has been amended as follows:

In claim 1, line 6, after the word "particles" insert "of the said compound"

The following is an examiner's statement of reasons for allowance:

Applicants have compared instant claimed composition with the closest prior art teachings and showed that employing the same techniques of tablet preparation i.e., wet granulation or direct compression, the prior art compositions result in either extremely hard or too soft compositions, the dissolution of which is incomplete. Whereas under the same conditions, instant free drug particles of the active compound result in complete and rapid dissolution and improved bioavailability, which is unexpected over the prior art teachings because the art of record does not suggest free drug particles of the instant active agent i.e., drug particles without absorption of drug on to a carrier in a formulation.

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."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 7.00 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. 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.

October 27, 2006

LAKSHMI S. CHANNAVAJJALA
PRIMARY EXAMINER
AU 1615

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/031,464	OREN ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

All Participants: **Status of Application:** _____

(1) *Lakshmi S. Channavajjala*. (3) _____.

(2) *James Napoli*. (4) _____.

Date of Interview: *25 October 2006* **Time:** _____

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:

Claims discussed:
on record

Prior art documents discussed:
US 6,841,167

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.
☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

LAKSHMI S. CHANNAVAJJALA
PRIMARY EXAMINER

(Examiner/SPE Signature) (Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed: Examiner informed attorney that instant claims would be allowable upon filing a terminal disclaimer over US patent 6,841,167 (already of record). Attorney agreed to file a TD. Further, examiner was authorized examiner to amend instant claim 1 to reflect that the particles in the claim refer to the active compound, by examiner's amendment.

Issue Classification	Application/Control No. 10/031,464	Applicant(s)/Patent under Reexamination OREN ET AL.
	Examiner Lakshmi S. Channavajjala	Art Unit 1615

ISSUE CLASSIFICATION

ORIGINAL		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
424	464	A	61	K	9	/20	A	61	K	9	/48
						/	A	61	K	9	/64

CROSS REFERENCES											
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)										
424	489	451	452	455							
	456										
514	250										

(Assistant Examiner) (Date)

(Legal Instruments Examiner) 10/31/06 (Date)

LAKSHMI S. CHANNAVAJJALA
PRIMARY EXAMINER
(Primary Examiner) (Date) 10/27/06

Total Claims Allowed: 32

O.G. Print Claim(s)	O.G. Print Fig.
1	-

☐ 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
1	1	27	31		61		91		121		151		181
2	2	28	32		62		92		122		152		182
3	3	29	33		63		93		123		153		183
4	4	30	34		64		94		124		154		184
	5	31	35		65		95		125		155		185
5	6	32	36		66		96		126		156		186
6	7		37		67		97		127		157		187
7	8		38		68		98		128		158		188
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9	10		40		70		100		130		160		190
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	26		56		86		116		146		176		206
	27		57		87		117		147		177		207
24	28		58		88		118		148		178		208
25	29		59		89		119		149		179		209
26	30		60		90		120		150		180		210

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/031,464	OREN ET AL.
Examiner	**Art Unit**
Lakshmi S. Channavajjala	1615

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date								
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/031,464	OREN ET AL.	
Examiner	**Art Unit**	
Lakshmi S. Channavajjala	1615	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
Interference search history printout		10/27/2006	LC

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
updated search on WEST-all data bases; STN-caplus, reg file	10/25/2006	LC

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 6930

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/031,464	04/29/2002 RULE	514	1614	29342/36230A

APPLICANTS

Peter L. Oren, Fishers, IN;
Neil R. Anderson, West Lafayette, IN;
Martha A. Kral, Indianapolis, IN;

** CONTINUING DATA ********** Verified

THIS APPLICATION IS A 371 OF PCT/US00/11130 04/26/2000
WHICH CLAIMS BENEFIT OF 60/146,924 08/03/1999

** FOREIGN APPLICATIONS ********** none

		STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed	☐ yes ☒ no	IN		26	1
35 USC 119 (a-d) conditions met	☐ yes ☒ no ☐ Met after Allowance				
Verified and Acknowledged	Examiner's Signature Initials				

ADDRESS

04743

TITLE

Beta-carboline pharmaceutical compositions

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
1128	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

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Certificate of Transmission
PETER L. OREN ET AL.	I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office today, **October 25, 2006**, to Examiner L. Channavajjala at facsimile number 571-273-0591
Serial No.: 10/031,464	
Filed: April 29, 2002	
For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**	
Attorney Docket No. 29342/36230A	
Group Art Unit: 1615	James J. Napoli Registration No. 32,361 Attorney for Applicants
Examiner: L. Channavajjala	

TRANSMITTAL OF TERMINAL DISCLAIMER TO OBVIATE A DOUBLE-PATENTING REJECTION OVER AN ISSUED PATENT

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

Sir:

In response to the telephonic interview with Examiner Channavajjala on October 25, 2006, applicants transmit a terminal disclaimer over U.S. Patent No. 6,841,167.

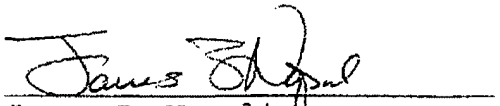
The Commissioner is hereby authorized to charge the $130.00 Terminal Disclaimer fee to Deposit Account No. 13-2855.

It is submitted that the claims are in proper form and for entry. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

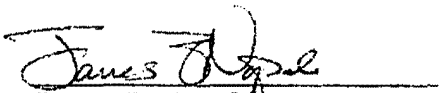
By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
October 25, 2006

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Certificate of Transmission
PETER L. OREN ET AL.	I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office today, October 25, 2006, to Examiner L. Channavajjala at facsimile number 571-273-0591
Serial No.: 10/031,464	
Filed: April 29, 2002	
For: β-CARBOLINE PHARMACEUTICAL COMPOSITIONS	
Attorney Docket No. 29342/36230A	
Group Art Unit: 1615	James J. Napoli
Examiner: L. Channavajjala	Registration No. 32,361 Attorney for Applicants

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE-PATENTING REJECTION OVER AN ISSUED PATENT

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

Sir:

The undersigned, having power of attorney from the assignee, Lilly ICOS LLC, has executed this document on behalf of petitioner, Lilly ICOS LLC. Petitioner is a Delaware corporation, 1209 Orange Street, Wilmington, Delaware 19801, and is the owner of 100% interest in the instant application, as shown by the assignment recorded May 8, 2002, at Reel 12877, Frame 0177. Petitioner hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §154 to §156 and

§173, as presently shortened by any terminal disclaimer of prior Patent No. 6,841,167. Petitioner also is the owner of 100% interest in U.S. Patent No. 6,841,167 as shown by the assignment recorded on April 15, 2002 at Reel 12818, Frame 0640. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and U.S. Patent No. 6,841,167 are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, petitioner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §154 to §156 and §173 of prior Patent No. 6,841,167, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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; further, these statements are made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereof.

The Commissioner is hereby authorized to credit any overpayment or charge any additional fees which may be required during the pendency of this application under 37 C.F.R. §1.16 or 37 C.F.R. §1.17 or under applicable rules (except payment of issue fees), to Deposit Account No. 13-2855. A copy of this transmittal is enclosed.

James J. Napoli
Registration No. 32,361

Dated: October 25, 2006

☒ The Commissioner is hereby authorized to charge the $130.00 Terminal Disclaimer fee to Deposit Account No. 13-2855.

MARSHALL, GERSTEIN & BORUN LLP
ATTORNEYS AT LAW
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606-6357
(312) 474-6300
FAX: (312) 474-0448

10/25/2006

FACSIMILE TRANSMISSION SHEET

TO: L. Channavajjala

U.S. Patent & Trademark Office

571 273 0591

FROM:

RE: Attorney Docket No. 29342/36230A; U.S. Serial No. 10/031,464

PAGES (INCLUDING THIS PAGE): 6

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If you do not receive all pages of this fax in good condition, please contact Janet Leathem at (312) 474-6300.

****

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/031,464	OREN ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 10/25/06	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
vbh (6,849,167)

U.S. Patent and Trademark Office

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)

04743 7590 11/03/2006

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

01/17/2007 WASFAW2 00000017 10031464

01 FC:1501 1400.00 OP
02 FC:8001 12.00 OP

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.

James J. Napoli	(Depositor's name)
James J. Napoli	(Signature)
11 January 2007	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,464	04/29/2002	Peter L. Oren	29342/36230A	6930

TITLE OF INVENTION: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$0	$0	$1400	02/05/2007

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHANNAVAJJALA, LAKSHMI SARADA	1615	424-464000

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 Marshall,
2 Gerstein &
3 Borun 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: LILLY ICOS LLC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Wilmington, Delaware

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 4

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 credit any overpayment, to Deposit Account Number 13-2855 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature James J. Napoli Date 11 January 2007

Typed or printed name James J. Napoli Registration No. 32,361

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.
10/031,464	02/27/2007	7182958	29342/36230A	6930

4743 7590 02/07/2007

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Extension under 35 U.S.C. 154 (b)
(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 0 day(s). Any patent to issue from the above-identified application will include an indication of the 0 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension is the filing date of the most recent CPA.

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 (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Peter L. Oren, Fishers, IN;
Neil R. Anderson, West Lafayette, IN;
Martha A. Kral, Indianapolis, IN;

10/031464

Cefc

Docket No.: 29342/36230A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Peter L. Oren et al.

Patent No.: 7,182,958

Issued: February 27, 2007

For: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 CFR 1.323

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted typographical errors which should be corrected.

On the First Page:

In the Assignment, line 5, Applicant error, "Lilly Icos LLC." should be -- Lilly ICOS LLC --.

In the Specification:

In the Amendment dated September 24, 2004, page 2, line 7, Applicant error, "derivatives" should be -- derivative --.

At page 16, line 4, Applicant error, "croscarmellulose" should be -- croscarmellose --.

The errors were found in the application as filed by applicant. Our check in the amount of $100.00 covering the fee set forth in 37 CFR 1.20(a) is enclosed.

The errors now sought to be corrected are inadvertent typographical errors the correction of which does not involve new matter or require reexamination.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 13-2855, under Order No. 29342/36230A.

Dated: October 15, 2007

Respectfully submitted,

By _____

James J. Napoli
Registration No.: 32,361
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicants

Docket No.: 29342/36230A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Peter L. Oren et al.

Patent No.: 7,182,958

Issued: February 27, 2007

For: BETA-CARBOLINE PHARMACEUTICAL COMPOSITIONS

REQUEST FOR CERTIFICATE OF CORRECTION
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Dear Sir:

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At page 16, line 4, Applicant error, "croscarmellulose" should be -- croscarmellose --.

The errors were found in the application as filed by applicant. Our check in the amount of $100.00 covering the fee set forth in 37 CFR 1.20(a) is enclosed.

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The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 13-2855, under Order No. 29342/36230A.

Dated: October 15, 2007

Respectfully submitted,

By _____

James J. Napoli
Registration No.: 32,361
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicants

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
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.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	7,182,958
APPLICATION NO.	:	10/031,464
ISSUE DATE	:	February 27, 2007
INVENTOR(S)	:	Peter L. Oren et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the First Page:

At field (73), "Lilly Icos LLC." should be -- Lilly ICOS LLC --.

In the Specification:

At Column 5, line 4, "derivatives" should be -- derivative --.

At Column 7, line 38, "croscarmellulose" should be -- croscarmellose --.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
James J. Napoli
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,182,958 B1
APPLICATION NO. : 10/031464
DATED : February 27, 2007
INVENTOR(S) : Peter L. Oren et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

Item (73), "Lilly Icos LLC." should be -- Lilly ICOS LLC --.

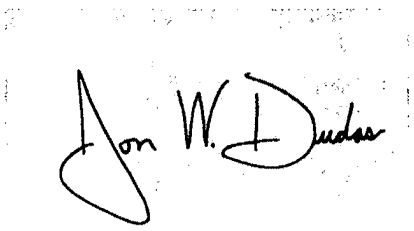
In the Specification:

Column 5, line 4, "derivatives" should be -- derivative --.

Column 7, line 38, "croscarmellulose" should be -- croscarmellose --.

Signed and Sealed this

Eighteenth Day of December, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Eastern District of NC on the following ☑ Patents or ☐ Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
5:10-CV-150-D1	4/19/2010	Eastern District of NC

PLAINTIFF	DEFENDANT
SYNTHON PHARMACEUTICALS, INC.	ELI LILLY AND COMPANY and ICOS CORPORATION

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,821,975	11/23/2004	ICOS CORPORATION
2	7,182,958	2/27/2007	ICOS CORPORATION
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
DENNIS P. IAVARONE, CLERK	Deborah A. Hunt	4/20/10

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

Trials@uspto.gov
Tel: 571-272-7822

Paper 7
Entered: August 4, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACTELION PHARMACEUTICALS LTD,
Petitioner,

v.

ICOS CORPORATION,
Patent Owner.

Case IPR2015-00561
Patent 7,182,958 B1

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Actelion Pharmaceuticals Ltd ("Petitioner") filed a Petition (Paper 1, "Pet.") to institute an *inter partes* review of claims 1–32 of US 7,182,958 B1 (Ex. 1003, "the '958 patent"). ICOS Corporation ("Patent Owner") timely filed a Preliminary Response. Paper 6 ("Prelim. Resp.").

For the reasons provided below, we determine that, having established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim, Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). We institute an *inter partes* review of claims 1–32 of the '958 patent.

Related Proceedings

According to the parties, the '958 patent is the subject of certain district court cases involving third parties. Pet. 1; Paper 4, 2. Petitioner concurrently filed a petition for an *inter partes* review of another patent owned by Patent Owner in IPR2015-00562 (U.S. Patent No. 6,821,975 B1). Paper 4, 2.

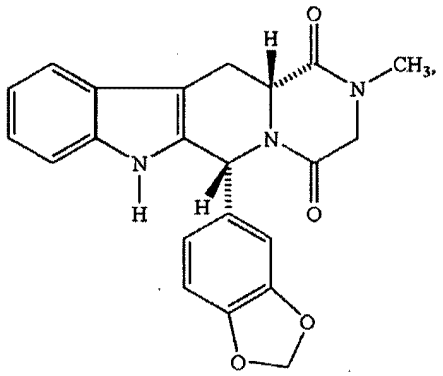
The '958 Patent

The '958 patent relates to formulations containing PDE5 inhibitors, specifically, β-carboline compounds, and their use in treating sexual dysfunction. Ex. 1003, Abstract, 1:14–20.

At the time of the '958 patent invention, because of the poor solubility of the many β-carboline compounds, prior art described the development of co-precipitate preparations of these compounds. *Id.* at 1:43–49. According to the '958 patent, however, the co-precipitate products have various

drawbacks, and thus, are "less than ideal for pharmaceutical formulations." *Id.* at 1:50–63.

The '958 patent discloses a pharmaceutical formulation comprising a compound of formula (I) and pharmaceutically acceptable salts and solvates thereof. *Id.* at 2:3–28. Formula (I) has the following structure:



Id. at 2:5–20. The '958 patent specifies that the compound of formula (I)[1] "preferably is provided as a free drug." *Id.* at 2:28–29. According to the '958 patent, its particular formulation of formula (I) has enhanced dosage uniformity, stability, and bioavailability. *Id.* at 3:65–4:4.

Illustrative Claims

Claim 1 is the sole independent claim challenged in the Petition. It reads:

> 1. A pharmaceutical formulation comprising an active compound having the structural formula [of formula (I),]
>
> wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles of the said compound have a particle size of less than about 40 microns; about 50% to about 85%, by weight, of a water-soluble

[1] The generic name of the compound of formula (I) is tadalafil. Pet. 4; Prelim. Resp. 6.

> diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

Claims 2–32 depend, directly or independently, from claim 1. Specifically, claims 2–19 and 24–26 are directed to pharmaceutical formulations. Claims 20–23 and 27–30 are directed to tablets comprising, or capsules encasing, the formulation of claim 1. Claims 31 and 32 are directed to methods of treating sexual dysfunction using the composition of any one of claims 1–23 and 28–30.

Asserted Ground of Unpatentability

Petitioner presents a single ground of unpatentability, asserting that claims 1–32 are unpatentable as obvious over the combination of Daugan,[2] Seth,[3] Butler,[4] and the common pharmaceutical knowledge evidenced in Wadke,[5] Rudnic,[6] and Banker.[7]

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[2] Daugan, WO 97/03675, published Feb. 6, 1997 (Ex. 1006, "Daugan").

[3] Seth et al., U.S. Patent No. 4,721,709, issued Jan. 26, 1988 (Ex. 1011, "Seth").

[4] Butler, WO 96/38131, published Dec. 5, 1996 (Ex. 1008, "Butler").

[5] Deodatt A. Wadke et al., Preformulation Testing, PHARMACEUTICAL DOSAGE FORMS: TABLETS 1–73 (Herbert A. Lieberman et al. eds., 2d ed., revised and expanded, Marcel Decker 1989) (Ex. 1014, "Wadke").

[6] Edward M. Rudnic & Mary Kathryn Kottke, Tablet Dosage Forms, MODERN PHARMACEUTICS 333–94 (Gilbert S. Banker & Christopher T. Rhodes eds., 3d ed., Marcel Decker 1996) (Ex. 1013, "Rudnic").

[7] Gilbert S. Banker & Neil R. Anderson, Tablets, THE THEORY AND PRACTICE OF INDUSTRIAL PHARMACY, 293, 324–29 (Leon Lachman et al.

In support of its patentability challenges, Petitioner relies on the Declaration of Dr. Harry G. Brittain (Ex. 1002).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, LLC, No. 2014-1301, 2015 WL 4097949, *8 (Fed. Cir. July 8, 2015). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

The parties agree that the '958 patent Specification expressly defines the terms "compound having the structural formula" and "free drug." Pet. 12–13; Prelim. Resp. 10. For purposes of this Decision, we adopt the following constructions as they are set forth in the Specification with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

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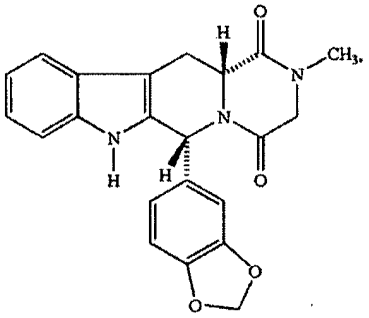
eds., 3d ed., Lea & Febiger 1986) (Ex. 1018, "Banker").

Claim Term	Construction
the structural formula 	formula (I), also known as: (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione; or (6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)pyrazino[2′,1′:6.1]pyrido[3,4-b]indole-1,4-dione (Ex. 1003, 2:3–26)
free drug	solid particles consisting essentially of the compound of structural formula (I), as opposed to the compound intimately embedded in a polymeric coprecipitate (Ex. 1003, 3:11–14)

35 U.S.C. § 325(d)

Patent Owner asks us to deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 29–45. According to Patent Owner, during prosecution of the '958 patent, the examiner allowed the challenged claims despite initially rejecting the claims as obvious over the combination of Daugan, Butler, and Seth. *Id.* at 33–38. Patent Owner asserts that Wadke, Rudnic, and Banker, which Petitioner presents as reflecting only the common pharmaceutical knowledge in the art, do not add new substance. *Id.* at 38–40.

During the prosecution, the applicants submitted an inventor declaration and argued unexpected results to overcome the obviousness rejection. Ex. 1005, 330–55. Petitioner challenges the experimental design presented in the declaration as deficient. Pet. 8–11. Petitioner seeks an opportunity to offer rebuttal evidence in a trial. *Id.* at 11.

The statute allows, but does not require, the Director to deny a petition if "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). We decline to exercise our discretion to deny the Petition on this basis in this case.

Patentability Analysis

Prior Art Disclosures

Daugan

Daugan identifies (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)pyrazino[2',1':6.1] pyrido[3,4-b]indole-1,4-dione as compound (A), a compound of the invention. Ex. 1006, 00005:24–25. Compound (A) is the same as the compound of formula (I) in the '958 patent, i.e., tadalafil.

Daugan teaches that tadalafil is useful for treating male or female sexual dysfunction. *Id.* at 00006:25–28. It also teaches formulating tadalafil with a pharmaceutically acceptable diluent, carrier, or excipient. *Id.* at 00007:15–21, 00007:32–36.

Butler

Butler teaches the preparation of solid dispersions of poorly water soluble drugs, and their use in pharmaceutical compositions. Ex. 1008, 00003:3–5. According to Butler, "[c]o-precipitation is a recognised technique for increasing the dissolution of poorly water soluble drugs." *Id.* at 00003:15–16.

According to Butler, tadalafil, referred to as "Compound A," is a poorly water soluble drug. *Id.* at 00006:15–18, 00007:4–5. Butler teaches

the process to prepare a solid dispersion of tadalafil, comprising co-precipitating Compound A and a pharmaceutically acceptable carrier or excipient. *Id.* at 00006:15–21, 00007:1–29, 00016:13–00017:16.

Seth

Seth teaches pharmaceutical compositions of hydrophobic drugs adsorbed onto carriers such as starch and/or microcrystalline cellulose. Ex. 1011, Abstract.

According to Seth, "when poorly soluble, hydrophobic drug substances are employed in the preparation of solid dosage forms such as tablets or capsules," their rates of dissolution and absorption are slow. *Id.* at 1:66–2:3. This limits the therapeutic utility if the drugs are to be administered orally for indications that require a rapid onset of therapeutic activity. *Id.* at 2:3–8. Seth teaches that methods that "finely grind or 'micronise' drug substances so as to reduce their particle size" may overcome such problems. *Id.* at 2:9–13. The grinding methods, however, also have some disadvantages. *Id.* at 2:13–20.

Seth teaches that

> The problem is solved by providing a dry powder pharmaceutical composition containing a hydrophobic, poorly soluble drug that is adsorbed on to a pharmaceutical carrier preferably an organic pharmaceutical carrier such as starch or cellulose and is characterised in that the drug is present in particulate form and that the drug particles have a mean particle size of less than 10 microns and a particle size distribution such that at least 95% of particles are smaller than 15 microns.

Id. at 4:44–52. According to Seth, its process is "applicable in general to almost all or most of the 'practically water insoluble drugs' so that they can

be easily formulated into solid dosage-forms showing a fast rate of dissolution and absorption." *Id.* at 3:59–63.

Wadke

Wadke teaches that "[i]t is now generally recognized that poorly soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided state than as a coarse material." Ex. 1014, 00007. According to Wadke, grinding poorly water-soluble materials increases dissolution rate. *Id.* Wadke suggests "[g]rinding should reduce coarse material to, preferably, the 10- to 40- μm range." *Id.* at 00007–08.

Obviousness over the Combination of Daugan, Seth, and Butler

Petitioner contends that claims 1–32 would have been obvious over the combination of Daugan, Seth, Butler, and the common pharmaceutical knowledge evidenced in Wadke, Rudnic, and Banker. Pet. 21–59. Based on the current record, we are persuaded that Petitioner has established a reasonable likelihood it would prevail on this basis.

Petitioner argues that an ordinary artisan would have had a reason to employ the teachings of Seth to modify Daugan. Pet. 23. Petitioner points to Butler for teaching that tadalafil is a poorly soluble drug. *Id.* Citing Dr. Brittain, Petitioner asserts that a slow dissolution rate results in poor absorption of a drug. *Id.* at 24 (citing Ex. 1002 ¶ 82). Petitioner refers to Seth for teaching that micronizing a drug is a frequently used method to overcome the problems of slow dissolution and absorption. *Id.* (citing Ex. 1011, 2:9–11). Seth teaches a dry powder pharmaceutical composition

of a hydrophobic, poorly soluble drug, wherein the drug is present in particulate form with a mean particle size of less than 10 microns and a particle size distribution such that at least 95% of particles are smaller than 15 microns. *Id.* at 22 (citing Ex. 1011, 4:44–52). Thus, according to Petitioner, modifying tadalafil, as taught in Daugan, with the teachings of Seth would have resulted in fine particles of tadalafil, such that 90% of the particles are less than about 40 microns, as recited in claim 1. *Id.* at 21–22.

Petitioner asserts that lactose is a widely employed water-soluble diluent. *Id.* at 26–27 (citing Ex. 1013, 00014; Ex. 1018, 00004). Thus, according to Petitioner, 70% by weight anhydrous lactose and 59% by weight lactose in tablet formulations, taught in examples A1 and B2 of Daugan, respectively, fall within the range of "about 50% to about 85%, by weight, of a water-soluble diluent," as required in claim 1. *Id.* at 26 (citing Ex. 1006, 00014, 00016).

For the other limitations of claim 1, Petitioner argues that (1) all examples in Daugan use magnesium stearate as a lubricant; (2) example B1 of Daugan uses povidone as a binder; and (3) example B1 of Daugan uses croscarmellose sodium and examples A1 and A2 use crospovidone as disingegrants. *Id.* at 29–32 (citing Ex. 1006, 00014–16).

In its Preliminary Response, Patent Owner does not dispute the teachings of these claim limitations in the prior art. Patent Owner, instead, counters that Petitioner fails to address a teaching or suggestion of an essential claim limitation—"free drug comprising particles" of tadalafil. Prelim. Resp. 13–19. We are not persuaded. Petitioner appears to rely on the prosecution history of the '958 patent, in which the examiner stated that Daugan meets the "free drug" limitation. Pet. 13 (citing Ex. 1005, 314,

which in turn cites Ex. 1006, 00014–00016). Patent Owner does not address this point in the Preliminary Response.

Rather, Patent Owner contends that Petitioner fails to address a motivation to prepare the "free drug comprising particles" in view of the contrary teachings in Butler and Seth. Prelim. Resp. 20–24. Patent Owner refers to Butler for teaching a co-precipitate formulation to increase the dissolution of tadalafil. *Id.* at 20 (citing Ex. 1008, Abstract, 3:15–18). Patent Owner argues Butler's approach is "the opposite" of a solution involving free drug particles. *Id.* According to Patent Owner, "Butler identified a problem, discovered an inventive solution that worked, and disclosed no further problem with tadalafil's solubility to be solved." *Id.* at 21. Petitioner, however, points to the teachings in Wadke that particle size reduction is "the most commonly employed practice" in addressing a slow dissolution rate. Pet. 23 (citing Ex. 1014, 00025). Patent Owner further contends that methods like that of Butler represent "the ultimate in size reduction." Prelim. Resp. 24 (citing Ex. 1014, 00007). Even if that were accurate, "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Based on the current record, we are not persuaded that the method taught in Butler would have deterred a person of ordinary skill in the art from improving the dissolution rate of tadalafil using the method described in, for example, Seth and Wadke.

Patent Owner also asserts that Seth teaches away from "free drug comprising particles" because it teaches "adsorbing [a] drug onto a 'closely associated' carrier first as part of a suspension to increase solubility." Prelim. Resp. 23. According to Patent Owner, "Seth's answer, forming an

intimate mixture of the drug with a carrier to increase solubility, is similar to Butler's intimately embedded co-precipitate with a solid dispersion including an inert carrier." *Id.* Patent Owner, however, does not point to persuasive evidence for support. As a result, we accord little weight to this conclusory statement.[8]

Patent Owner argues that Wadke discloses "a long list of micronization problems" that "undermin[e] the premise of the petition that it would have been obvious to micronize []'free drug comprising particles' of tadalafil." Prelim. Resp. 25 (citing Ex. 1014, 00007, 00008). Based on the current record, we are not persuaded. For example, according to Patent Owner, Wadke teaches that "micronizing leads to '**undesirable properties.**'" *Id.* (citing Ex. 1014, 00007). In fact, Wadke states that such is the case only "if materials become too fine." Ex. 1014, 00007. Wadke explains that "it is important to decide on a desired size range," and recommends the preferred size in the range of 10 to 40 microns, within the "less than about 40 microns" range recited in claim 1. *Id.* at 00007–08. Based on the current record, we are not persuaded that a skilled artisan would not have considered micronization to improve the solubility of tadalafil because of the problems allegedly associated therewith.

In sum, based on the current record, we conclude Petitioner has established a reasonable likelihood it would prevail in showing that claim 1 would have been obvious over the combination of Daugan, Seth, Butler, and the common pharmaceutical knowledge evidenced in Wadke, Rudnic, and

[8] We understand that Patent Owner is prohibited from presenting new testimonial evidence as of right to support its Preliminary Response. *See* 37 C.F.R. § 107(c). There is no such limitation once the trial is instituted.

Banker. Claims 2–32 depend from claim 1. After considering the Petition, Dr. Brittain's testimony, and accompanying evidence (*see, e.g.*, Pet. 33–40; Ex. 1002 ¶¶ 74–79), we also are persuaded that Petitioner has made a sufficient showing regarding the additional limitations of those claims. Therefore, we institute *inter partes* review of claims 1–32.

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1–32 of the '958 patent.

The Board has not made a final determination on the patentability of any challenged claim or the construction of any term.

ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to whether claims 1–32 of the '958 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Daugan, Seth, Butler, and the common pharmaceutical knowledge evidenced in Wadke, Rudnic, and Banker; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '958 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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