



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

<b>(51) International Patent Classification<sup>7</sup> :</b>  <b>A61K 31/13, 31/135</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/10551</b>  <b>(43) International Publication Date:</b> 2 March 2000 (02.03.00)
<b>(21) International Application Number:</b> PCT/US99/19167 <b>(22) International Filing Date:</b> 23 August 1999 (23.08.99)  <b>(30) Priority Data:</b> 60/097,665            24 August 1998 (24.08.98)    US 60/099,306            2 September 1998 (02.09.98)    US Not furnished            11 August 1999 (11.08.99)    US  <b>(71) Applicant:</b> SEPRACOR INC. [US/US]; 111 Locke Drive, Marlborough, MA 01752 (US).  <b>(72) Inventors:</b> JERUSSI, Thomas, P.; 19 Garvey Road, Framing- ham, MA 01701 (US). SENANAYAKE, Chrisantha, H.; 11 Old Farm Circle, Shrewbury, MA 01545 (US). FANG, Qun, K.; 35 Atwood Street, Wellesley, MA 02181 (US).  <b>(74) Agents:</b> LAWRENCE, Stanton, T., III et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).	<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 21 September 2000 (21.09.00)	
<b>(54) Title:</b> METHODS OF USING AND COMPOSITIONS COMPRISING DOPAMINE REUPTAKE INHIBITORS		
<b>(57) Abstract</b>  <p>Methods are disclosed for the treatment and prevention of disorders and conditions including, but are not limited to, erectile dysfunction, affective disorders, weight gain, cerebral functional disorders, pain, obsessive-compulsive disorder, substance abuse, chronic disorders, anxiety, eating disorders, migraines, and incontinence. The methods comprise the administration of a dopamine reuptake inhibitor and optionally an additional pharmacologically active compound. Pharmaceutical compositions and dosage forms are also disclosed that comprise a dopamine reuptake inhibitor and optionally an additional pharmacologically active compound. Preferred dopamine reuptake inhibitors are racemic or optically pure sibutramine metabolites like desmethylsibutramine and didesmethylsibutramine and pharmaceutically acceptable salts, solvates, and clathrates thereof. Preferred additional pharmacologically active compounds include drugs that affect the central nervous system, such as 5-HT<sub>3</sub> antagonists.</p>		

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/19167

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/13 A61K31/135

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 7 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	WO 95 21615 A (BOOTS CO PLC ;BUCKETT WILLIAM ROGER (GB)) 17 August 1995 (1995-08-17) abstract; claims 1-3,6-16; example 3 page 3, line 24 -page 4, line 24 page 20, paragraph 3 ---	1-7, 27-29, 59-67
P, X	WO 99 33450 A (KNOLL AG ;JACKSON HELEN CHRISTINE (GB); HEAL DAVID JOHN (GB)) 8 July 1999 (1999-07-08)  abstract page 2, line 1-10  ---  -/--	1-7,25, 26,42, 43,49, 50,57, 59-69, 72-77



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
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- "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
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Date of the actual completion of the international search

16 May 2000

Date of mailing of the international search report

20/06/2000

Name and mailing address of the ISA

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

A. Jakobs

**INTERNATIONAL SEARCH REPORT**

Inte lonal Application No

PCT/US 99/19167

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 13034 A (KNOLL AG ; JONES STEPHEN PAUL (GB); KELLY PETER FINIAN (GB)) 2 April 1998 (1998-04-02)</p> <p>abstract</p>	<p>1-7, 25, 26, 42, 43, 49, 50, 57, 59-69, 72-77</p>
X	<p>WO 88 06444 A (BOOTS CO PLC) 7 September 1988 (1988-09-07)</p> <p>abstract page 1, line 1 -page 3, line 3; claims 1-8</p>	<p>1-7, 27-30, 59-69, 72-77</p>
A	<p>US 4 939 175 A (UKAI KIYOHARU ET AL) 3 July 1990 (1990-07-03)</p> <p>the whole document</p>	<p>1-7, 27-30, 59-69, 72-77</p>
X	<p>LUSCOMBE G P ET AL: "THE CONTRIBUTION OF METABOLITES TO THE RAPID AND POTENT DOWN-REGULATION OF RAT CORTICAL BETA-ADRENOCEPTORS BY THE PUTATIVE ANTIDEPRESSANT SIBUTRAMINE HYDROCHLORIDE" NEUROPHARMACOLOGY, GB, PERGAMON PRESS, OXFORD, vol. 28, no. 2, 1 February 1989 (1989-02-01), pages 129-134, XP000613753 ISSN: 0028-3908 abstract</p>	<p>1-7, 20-24, 27, 29, 44, 59-66, 75-77</p>
X	<p>DE 32 12 682 A (BOOTS CO LTD) 21 October 1982 (1982-10-21)</p> <p>abstract page 18, paragraph 1; claims 44-46 page 24, paragraph 1; examples 1C, 4K,</p>	<p>1-7, 20-24, 27, 29, 44, 59-66, 75-77</p>
X	<p>HEAL, D. J. ET AL: "A comparison of the effects on central 5-HT function of sibutramine hydrochloride and other weight-modifying agents" BR. J. PHARMACOL. (1998), 125(2), 301-308, XP000905054 abstract</p>	<p>1-7, 25, 26, 42, 43, 49, 50, 57, 59-69, 72-77</p>
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/19167

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEETHAM, S. C. ET AL: "'3H!Paroxetine binding in rat frontal cortex strongly correlates with '3H!5-HT uptake: effect of administration of various antidepressant treatments" NEUROPHARMACOLOGY (1993), 32(8), 737-43 , XP000905163 abstract; table 1 ---	1-7, 20-24, 27,29, 44, 59-66, 75-77
X	JEFFERY, JAMES E. ET AL: "Synthesis of sibutramine, a novel cyclobutylalkylamine useful in the treatment of obesity, and its major human metabolites" J. CHEM. SOC., PERKIN TRANS. 1 (1996), (21), 2583-2589 , XP002137121 page 2583, column 1, paragraphs 1-3 ---	1-7,25, 26,42, 43,49, 50,57, 59-69, 72-77
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Y	GRAY, A. M.; SPENCER, P. S. J.; SEWELL, R. D. E.: "The involvement of the opioidergic system in the antinociceptive mechanism of action of antidepressant compounds" BR. J. PHARMACOL., vol. 124, no. 4, 1998, pages 669-674, XP000909217 abstract ---	30-32
Y	WO 94 00047 A (SEPRACOR INC) 6 January 1994 (1994-01-06) abstract page 2, paragraph 2 ---	20-24, 27-29,44
X	EP 0 781 561 A (FUJISAWA PHARMACEUTICAL CO) 2 July 1997 (1997-07-02) page 2, line 36 -page 3, line 27; claims 1-3 -----	8,14-16

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 19167

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-59,62-77 relate to a compound/product/use defined (inter alia)

by reference to the following parameter(s):

P1: disorder or condition ameliorated by inhibition of neuronal monoamine uptake.

P2: 5-HT3 antagonist.

P3: dopamine reuptake inhibitor.

P4: antiemetic agent.

P5: selective serotonin reuptake inhibitor.

P6: hypnotics and sedatives.

P7: drugs useful in treating psychiatric disorders.

P8: CNS stimulants.

P9: dopamine receptor agonists

P10: antimonic agent (sic ).

P11: antipanic agents.

P12: cardiovascular agents.

P13: antivirals, antibiotics, antifungals, antineoplastics.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Furthermore the term "sibutramine metabolite" is not clear in the present context since it is not clear into which compounds sibutramine is metabolised by or in the human body.

The term "chronic disorder" is not clear.

Consequently, the search has been restricted to the compounds and diseases specifically mentioned in the claims with due regard to the description and the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/19167

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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