

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
6 March 2008 (06.03.2008)

PCT

(10) International Publication Number  
**WO 2008/027395 A3**

(51) International Patent Classification:

A61K 47/10 (2006.01) A61K 31/5513 (2006.01)  
A61K 47/14 (2006.01) A61P 25/08 (2006.01)  
A61K 47/22 (2006.01)

(21) International Application Number:

PCT/US2007/018942

(22) International Filing Date: 27 August 2007 (27.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/840,568 28 August 2006 (28.08.2006) US

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(81) Designated States (unless otherwise indicated, for every

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

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

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

17 April 2008

(54) Title: PHARMACEUTICAL COMPOSITIONS OF BENZODIAZEPINES AND METHODS OF USE THEREOF

(57) Abstract: The present invention includes benzodiazepine compositions formulated for intranasal administration, comprising a binary solvent system comprising a first solvent in which the benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which the benzodiazepine is less soluble. The compositions of the present invention may be used to treat a variety of disorders including, but not limited to, panic attacks, muscle spasms, anxiety, and seizures. In one aspect, the present invention relates to a fast-acting, clonazepam composition for transnasal administration that can be used for the treatment of seizure clusters.



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# INTERNATIONAL SEARCH REPORT

International application No

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## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K47/10 A61K47/14 A61K47/22 A61K31/5513 A61P25/08

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

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

EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 656 303 A (PARKE DAVIS [FR]) 28 June 1991 (1991-06-28) page 1, lines 5-10 page 2, lines 16-32 page 3, line 25 - page 4, line 3 claims 1-6	1-19, 21, 24
X	WO 2004/004783 A (FOSCAMA BIOMED CHIM FARMA [IT]) 15 January 2004 (2004-01-15)  page 1, lines 6-25 page 8, lines 16-25 page 9, line 32 - page 11, line 6 page 14, line 14 - page 15, line 4 page 18, lines 5-14 claims 1-6, 11, 12  ----- -/--	1-13, 15-19, 21, 24



Further documents are listed in the continuation of Box C.



See patent family annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier 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

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\*&\* document member of the same patent family

Date of the actual completion of the international search

13 February 2008

Date of mailing of the international search report

25/02/2008

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/018942

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 693 608 A (BECHGAARD ERIK [DK] ET AL) 2 December 1997 (1997-12-02) column 3, line 43 - column 4, line 22 column 5, lines 32-41 column 6, lines 14-41 column 6, line 66 - column 7, line 4 column 7, line 9 - column 8, line 46 column 9, lines 17-26 column 15 - column 16; examples 2,3 column 16 - column 19; examples 6-8,11 column 27 - column 30; tables 1-4 column 31, lines 45-64	1-24
X	& WO 91/16929 A (NOVONORDISK AS [DK]) 14 November 1991 (1991-11-14) cited in the application -----	1-24
X	US 2006/153905 A1 (CARRARA R D N [CH] ET AL) 13 July 2006 (2006-07-13) page 1, paragraph 2 page 4, paragraphs 31-34,49 page 5, paragraphs 59,65 page 6, paragraphs 69,70 page 6, paragraph 73 - page 7, paragraph 73 page 8, paragraph 81 page 11; examples 28-30 -----	1-24
X	WO 02/11768 A (ANTARES PHARMA IPL AG [CH]) 14 February 2002 (2002-02-14) page 9, lines 4-16 page 10, lines 9,10 page 21 - page 23; examples 23-28,30 -----	1-24
X	WO 01/06987 A (SK CORP [US]) 1 February 2001 (2001-02-01) page 5, lines 6-29 page 8 - page 16; examples 3-9	1,4-9, 12-24
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	-/--	

## INTERNATIONAL SEARCH REPORT

International application No

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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>PUGLIA C ET AL: "Evaluation of in vitro percutaneous absorption of lorazepam and clonazepam from hydro-alcoholic gel formulations"</p> <p>INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 228, no. 1-2, 2001, pages 79-87, XP002467561</p> <p>abstract</p> <p>page 80, right-hand column, last paragraph</p> <p>- page 81, left-hand column, paragraph 1</p> <p>page 81; table 1</p> <p>-----</p>	<p>1-11,13, 15-19,21</p>
X	<p>CRANKSHAW D P ET AL: "THE EFFECT OF SOLVENTS ON THE POTENCY OF CHLORDIAZEPOXIDE, DIAZEPAM, MEDAZEPAM AND NITRAZEPAM"</p> <p>JOURNAL OF PHARMACY AND PHARMACOLOGY, LONDON, GB, vol. 23, no. 5, 1971, pages 313-321, XP008088376</p> <p>ISSN: 0022-3573</p> <p>abstract</p> <p>page 314, paragraph 1-3</p> <p>-----</p>	<p>1-9,13, 14, 16-19, 21,24</p>
X	<p>WO 2004/110403 A (SK CORP [KR])</p> <p>23 December 2004 (2004-12-23)</p> <p>cited in the application</p> <p>page 1, paragraph 1</p> <p>page 3, paragraph 8</p> <p>page 4; table 1</p> <p>page 4, paragraph 16 - page 5, paragraph 16</p> <p>-----</p>	<p>1,4-9, 12-14, 16-24</p>
X	<p>US 2005/163719 A1 (DUGGER HARRY A III [US] ET AL) 28 July 2005 (2005-07-28)</p> <p>-----</p> <p>page 1, paragraph 11</p> <p>page 3, paragraph 34</p> <p>page 5, paragraph 69</p> <p>page 12; example 13</p> <p>-----</p>	<p>1,4-9, 12-14, 16-19, 21,24</p>
X	<p>WO 2006/075123 A (CAMURUS AB [SE])</p> <p>20 July 2006 (2006-07-20)</p> <p>-----</p> <p>page 44; example 25</p> <p>-----</p> <p style="text-align: center;">-/--</p>	<p>1,4-9, 12-14, 16-24</p>

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/018942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2006/122217 A (UNIV MINNESOTA [US]) 16 November 2006 (2006-11-16) page 1, paragraph 2 page 6, paragraphs 14, 15 page 7, paragraph 19 page 8, paragraph 26 page 11, paragraph 56 - page 12, paragraph 59 page 28, paragraph 171-174 claims 1-57 -----	1-4, 6-9, 13-24

# INTERNATIONAL SEARCH REPORT

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

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

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 22 and 23 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 composition.
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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

### Remark on Protest

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

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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