



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/52, 31/575</p>	<p>A3</p>	<p>(11) International Publication Number: WO 99/61010 (43) International Publication Date: 2 December 1999 (02.12.99)</p>
<p>(21) International Application Number: PCT/EP99/03138 (22) International Filing Date: 7 May 1999 (07.05.99) (30) Priority Data: 98250177.7 26 May 1998 (26.05.98) EP (71) Applicant (for all designated States except US): SCHERING AKTIENGESELLSCHAFT [DE/DE]; D-13342 Berlin (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): HEGELE-HARTUNG, Christa [DE/DE]; Wöllenbeck 101, D-45470 Mülheim/Ruhr (DE). CAM, Quoc-Lam [DE/DE]; Am Schäfersee 15A, D-13407 Berlin (DE).</p>	<p>(81) Designated States: 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, US, UZ, VN, YU, 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).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 27 April 2000 (27.04.00)</p>	
<p>(54) Title: TREATMENT OF INFERTILITY WITH CAM-INCREASING COMPOUNDS ALONE OR IN COMBINATION WITH AT LEAST ONE MEIOSIS-STIMULATING COMPOUND</p>		
<p>(57) Abstract</p> <p>The present invention relates to a pharmaceutical composition comprising c-AMP-increasing compounds in low dose and at least one meiosis-stimulating compound for the treatment of infertility and to the use of low dose c-AMP-increasing compounds alone or in combination with at least one meiosis-stimulating compound to increase the rate of fertilization in a mammal and for the preparation of medicaments. The preferred c-AMP-increasing compound is Hypoxanthine. The meiosis-stimulating compound is FF-MAS (4,4-dimethyl-5alpha-cholest-8,14,24-trien-3beta-ol).</p>		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03138

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/52 A61K31/575

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	<p>BYSKOV A G ET AL: "CHEMICAL STRUCTURE OF STEROLS THAT ACTIVATE OOCYTE MEIOSIS" NATURE, GB, MACMILLAN JOURNALS LTD. LONDON, vol. 374, no. 6522, 6 April 1995 (1995-04-06), pages 559-562, XP002043016 ISSN: 0028-0836 cited in the application page 559, column 1 page 560, column 1, paragraphs 2,3; figure 1 page 562, column 1, paragraph 3 -column 2, paragraph 2</p>	1-33

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

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- "E" earlier document but published on or after the international filing date
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- "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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Date of the actual completion of the international search

1 March 2000

Date of mailing of the international search report

08/03/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03138

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 00235 A (NOVONORDISK AS ;BYSKOV ANNE GRETE (DK); ANDERSEN CLAUS YDING (DK);) 4 January 1996 (1996-01-04) abstract page 4, paragraph 8 -page 6, paragraph 4; examples 10,11 page 9, line 26 claims 1-6,31-36; tables 5,6	1-33
X	WO 96 27658 A (NOVONORDISK AS ;GUDDAL ERLING (DK); BYSKOV ANNE GRETE (DK); GROENV) 12 September 1996 (1996-09-12) abstract page 10, line 24-27 page 13, paragraph 1	1-33
X	WO 98 04366 A (CAULDRON LP) 5 February 1998 (1998-02-05) abstract; claims 1,2,9	1-3, 5-10, 12-17, 19-24, 26-31,33
X	WIERSMA A ET AL: "SPECIFIC PHOSPHODIESTERASE 3 INHIBITORS PREVENT THE RESUMPTION OF MEIOSIS IN MOUSE OOCYTES IN VITRO" BIOLOGY OF REPRODUCTION,US,ORLANDO, FL, vol. 56, no. SUPPL. 01, 1997, page 91 XP000874782 ISSN: 0006-3363 abstract	1-3, 5-10, 12-17, 19-24, 26-31,33
X	DIENHART, MARY K. ET AL: "Cyclic AMP reversal of hypoxanthine-arrested preimplantation mouse embryos is EDTA-dependent" ZYGOTE (1996), 4(2), 129-137 , XP000874771 abstract page 130, column 1, paragraph 2 -column 2, paragraph 2; figure 6	1-3, 5-10, 12-17, 19-24, 26-31,33
X,P	RUAN, BENFANG ET AL: "Sterols affecting meiosis: novel chemical syntheses and the biological activity and spectral properties of the synthetic sterols" J. LIPID RES. (1998), 39(10), 2005-2020 , XP000874959 abstract; figure 6	1-33
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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>WARIKOO P K ET AL: "Hypoxanthine and cyclic adenosine 5'-monophosphate maintain meiotic arrest of rhesus monkey oocytes in vitro." FERTILITY AND STERILITY, (1989 MAY) 51 (5) 886-9. , XP000874960 abstract</p>	<p>1-3, 5-10, 12-17, 19-24, 26-31,33</p>
X	<p>CARROLL J ET AL: "Effect of dibutyryl cyclic adenosine monophosphate on granulosa cell proliferation, oocyte growth and meiotic maturation in isolated mouse primary ovarian follicles cultured in collagen gels." JOURNAL OF REPRODUCTION AND FERTILITY, (1991 MAY) 92 (1) 197-207. , XP000874962 abstract</p>	<p>1-3, 5-10, 12-17, 19-24, 26-31,33</p>
X	<p>OTTESEN, JAN L. ET AL: "The effect of meiosis activating sterol (MAS) and some oxysterols on the resumption of meiosis in mouse oocytes cultured in vitro." BIOLOGY OF REPRODUCTION, (1997) VOL. 56, NO. SUPPL. 1, PP. 97. MEETING INFO.: THIRTIETH ANNUAL MEETING OF THE SOCIETY FOR THE STUDY OF REPRODUCTION PORTLAND, OREGON, USA AUGUST 2-5, 1997 , XP000874956 abstract</p>	<p>1-33</p>
X,P	<p>WIERSMA, A. ET AL: "Phosphodiesterase 3 inhibitors suppress oocyte maturation and consequent pregnancy without affecting ovulation and cyclicity in rodents" J. CLIN. INVEST. (1998), 102(3), 532-537 , XP000874944 abstract; table 1 page 533, column 2, paragraph 8 -page 534, column 2, paragraph 1</p>	<p>1-3, 5-10, 12-17, 19-24, 26-31,33</p>
X	<p>HARADA, M. ET AL: "Bovine oocytes from early antral follicles grow to meiotic competence in vitro: Effect of FSH and hypoxanthine." THERIOGENOLOGY, (1997) VOL. 48, NO. 5, PP. 743-755. , XP000874856 abstract</p>	<p>1-3, 5-10, 12-17, 19-24, 26-31,33</p>
X	<p>EP 0 196 530 A (CTA FINANZ AG) 8 October 1986 (1986-10-08)</p> <p>abstract; claims 1,2</p>	<p>1-3, 5-10, 12-17, 19-24, 26-31,33</p>
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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	<p>US 5 882 928 A (MOSES RUTH MIRIAM) 16 March 1999 (1999-03-16)</p> <p>abstract; claims 1-5</p>	<p>1-3, 6-9, 12-16, 19-23, 26-30, 33</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/03138

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:
Remark: Although claim(s) 26-32
is(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. 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:
see FURTHER INFORMATION PCT/ISA/210
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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 1-3,6-9,12-16,19-23,26-30,33 relate to a compound/composition/method/use defined (inter alia) by reference to the following parameter(s):

P1: c-AMP-increasing compound.

P2: unspecific PDE-inhibitors.

P4: synthetic membrane permeable cAMP.

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. Consequently, the search has been restricted to the compounds specifically mentioned in the claims with due regard to the description.

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

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9600235 A	04-01-1996	AU 694240 B	16-07-1998
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