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- (21) International Application Number: PCT/US01/06535 (81) Designated States (*national*): 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, UZ, VN, YU, ZA, ZW.
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- (26) Publication Language: English (71) Applicants: **PRAECIS PHARMACEUTICALS INCORPORATED** [US/US]; 830 Winter Street, Waltham, MA 02451 (US). **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1789 (US).
- (72) Inventors: **GARNICK, Marc, B.**; 140 Dudley Street, Brookline, MA 02146 (US). **MARTHA, M., Paul, Jr.**; 101 Hill Street, Topsfield, MA 01983 (US). **MOLIN- EAUX, Christopher, J.**; 23 Treotrop Avenue, San Mateo, CA 94402 (US). **DE PAOLI, Alex**; 645 Stoddard Lane, Santa Barbara, CA 93108 (US).
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**WO 01/64236 A3**

(54) Title: METHODS FOR TREATING FSH RELATED CONDITIONS WITH GnRH ANTAGONISTS

(57) Abstract: Methods for treating FSH related conditions, such as prostatic intraepithelial neoplasia, pedophilia, infertility, or vaginal bleeding, with GnRH antagonists are disclosed. The methods of the invention generally feature administering to a subject a GnRH antagonist suitable for (*in vivo* administration and able to reduce both plasma FSH and LH levels in a subject, in an amount or in a formulation effective to reduce plasma FSH levels in the subject to a symptom alleviating level. In vitro fertilization and male contraceptive methods are also provided.

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/06535

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/09 A61P5/04 A61P5/24 A61P15/00 A61P35/00  
A61P43/00 A61P43/00 //(A61K38/09,31:568)

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)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 843 901 A (ROESKE ROGER W) 1 December 1998 (1998-12-01) cited in the application	1-7, 41-44, 47-53
Y	the whole document especially column 13 lines 53-66, column 17 lines 15-25 and claims 1-5	8-14, 35-40
Y	--- NEWLING DON: "PIN I-III: When should we interfere?" EUROPEAN UROLOGY, vol. 35, no. 5-6, May 1999 (1999-05), pages 504-507, XP001024957 ISSN: 0302-2838 the whole document especially page 504 left-handed column lines 17-23 --- -/--	8-14, 35-40

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

9 October 2001

Date of mailing of the international search report

14 01. 2002

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

Stein, A

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/06535

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>US 5 968 895 A (MOLINEAUX CHRISTOPHER J ET AL) 19 October 1999 (1999-10-19) cited in the application the whole document especially column 5 lines 2-21, column 9 lines 24-60 and claims 1,10,12,27-31</p> <p>---</p>	1-7, 41-53
X	<p>US 5 470 947 A (KUBOTA MINORU ET AL) 28 November 1995 (1995-11-28) cited in the application column 3, line 65 - line 11 column 5, line 61 -column 6, line 7 column 14, line 45 -column 16, line 60 tables 7-13 claims 1-42</p> <p>---</p>	1-7, 47-53
X	<p>BEHRE HERMANN M ET AL: "Sustained suppression of serum LH, FSH and testosterone and increase of high-density lipoprotein cholesterol by daily injections of the GnRH antagonist cetrorelix over 8 days in normal men." CLINICAL ENDOCRINOLOGY, vol. 40, no. 2, 1994, pages 241-248, XP001024970 ISSN: 0300-0664 the whole document</p> <p>---</p>	1-6, 47-53
X	<p>MENON MANI ET AL: "Abarelix (PPI-149), a novel and potent GnRH antagonist, induces a rapid and profound reduction in testosterone and PSA in advanced prostate cancer patients (PrCa)." JOURNAL OF UROLOGY, vol. 159, no. 5 SUPPL., May 1998 (1998-05), page 334 XP001024926 93rd Annual Meeting of the American Urological Association, Inc.; San Diego, California, USA; May 30-June 4, 1998 ISSN: 0022-5347 the whole document</p> <p>---</p>	1-7, 41-43, 47-51,53
X	<p>WO 97 44037 A (GOULET MARK ;DEVITA ROBERT J (US); MERCK &amp; CO INC (US); WYVRATT MA) 27 November 1997 (1997-11-27) page 1, line 3 - line 26 page 3, line 21 -page 4, line 3 page 29, line 10 - line 29 claim 13</p> <p>-----</p>	1-8, 47-53

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/06535

## 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:  
  
Restricting the search to the first subject of the NON-UNITY claims 1-14 and 35-53, although they are directed to a method of treatment of the human/animal body, have been searched based on the alleged effects of the compound/composition.
2.  Claims Nos.: 1-14,35-37,41-53 (all partially)  
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 sheet 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:

see additional sheet

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.:  
  
1-8, 35-53 (all partially); 9-14 (completely)

### 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

Claims Nos.: 1-14,35-37,41-53 (all partially)

With restriction to the first subject of the NON-UNITY claims 1-14,35-37 and 45-53 relate to compounds defined by reference to a desired property, namely their antagonistic effect on GnRH. However these claims do not contain any structural or essential characteristics of the compounds. The claims cover all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds disclosed in claims 38-40 and more specifically disclosed in claims 41-44 of the application. Additionally the general term GnRH antagonist has been searched.

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8, 35-53 (all partially), 9-14

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the treatment of neoplastic conditions including prostatic intraepithelial neoplasia, prostate cancer, ovarian cancer, breast cancer, testicular cancer, pituitary gonadotropin tumors.

2. Claims: 1-8, 35-53 (all partially), 15-25

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the treatment of disorders specifically related to women including vaginal bleeding, endometriosis, uterine fibroids, premenstrual syndrome, polycystic ovary syndrome, ovarian cysts.

3. Claims: 1-8, 35-53 (all partially), 32-34

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the modulation of libido including the treatment of pedophilia.

4. Claims: 1-7, 41-53 (all partially)

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the treatment of precocious puberty.

5. Claims: 1-7, 41-53 (all partially)

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the treatment benign prostate hypertrophy.

6. Claims: 1-6, 41-53 (all partially), 26-31

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the contraception in male.

7. Claims: 1-7, 41-53 (all partially)

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the treatment of disorders related to an LH/FSH ratio imbalance.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

8. Claims: 1-7,41-53 (all partially)

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the treatment of thyroid related disorders.

9. Claims: 1-6, 41-53 (all partially), 59

The use of GnRH antagonists for the preparation of a pharmaceutical composition for the reduction of FSH levels.

10. Claims: 1-8, 41-53 (all partially), 54-58

The use of GnRH antagonists for in vitro fertilization and therewith the treatment of infertility.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/06535

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