PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/48 — A1

(11) International Publication Number: **WO 00/54776**

(43) International Publication Date: 21 September 2000 (21.09.00)

(21) International Application Number: PCT/IB99/00448

(22) International Filing Date: 17 March 1999 (17.03.99)

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(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), 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, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, 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).

Published
With international search report.
With amended claims.

(54) Title: USE OF PROLACTIN INHIBITORS FOR THE TREATMENT OF FERTILITY PROBLEMS IN ANIMAL SPECIES

(57) Abstract

The present invention is concerned with the treatment of fertility problems using a prolactin inhibitor in animals species, especially in cows. Further objects of the present invention are a method for a treatment of fertility problems and a method for the preparation of a medicament with said prolactin inhibitor.

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USE OF PROLACTIN INHIBITORS FOR THE TREATMENT OF FERTILITY PROBLEMS IN ANIMAL SPECIES

The present invention is concerned with the use of a medicament in the treatment of fertility problems in various animal species. Furthermore the invention is concerned with a method for a treatment of fertility problems with said medicament.

The postpartum period (PP) is associated with fertility problems in many species (1). In the cow the problem has been highlighted some time ago (2). Allusion has been made at that time to undernutrition. However undernutrition is not specific for the postpartum period. In the cow the problem is referred to as lactational anoestrus (Eigenmann, J.E.). Such cows on rectal palpation exhibit a corpus luteum persistens, an ovarian cyst or nothing (Acyclia).

Anoestrus by a Swiss study has been recognized to be the biggest problem in large animal practice (3). Current treatment is empiric, cost expensive and not invariably successful. This treatment includes one or two visits by the veterinarian, rectal palpation and administration of Gestagens. Gestagens in this condition are believed to exert a negative influence on pituitary function and thereby induce a rebound phenomenon at the end of their action. Gestagens include intravaginal devices or oral forms. Intravaginal devices often induce vaginitis and oral forms are time consuming.

Moreover, this Gestagen treatment which is also called synchronization method is derived from the synchronization of normal young.animals. In cows undergoing Gestagen treatment a new oestrus should appear approximately 3-10 days after withdrawal. Not

uncommonly prostaglandin F2α is administered in order to remove any residual corpus luteum tissue. Hence the treatment is expensive, nonspecific and most likely unsuccessful in many cases. 30 - 40% of premature slaughtering is due to unresolved fertility problems (3).

At any rate the cause of the problem remains obscure. Epidemiologic studies have shown that the problem is related to the 60-day milk yield. The higher initial milk secretion the higher the problems (4) suggesting that it must be a metabolic or hormonal factor which on one hand increases milk production but on the other hand decreases fertility. This study estimates the problem up to 15% of the population. It is believed that the common denominator to all problems is an absolute or relative lack of LH secretion.

In addition fertility problems increase in a square function in relation to milk increase (5). Although prolactin, which is important in the development of the mammary gland, is said by some veterinarians to be of no importance in milk production there are no good data to reject the hypothesis that specifically in the postpartum period prolactin induces and/or maintains a high milk yield. It is strongly believed that it must be Prolactin which inhibits LH-secretion leading to ovarian dysfunction (6, 7, 8).

Indeed in human prolactinoma there is significant ovarian dysfunction (lack of LH-secretion). Careful literature search shows that there have been prolactin (besides other hormones) determinations throughout lactation in a high milk yield breed versus a low milk yield breed. Interestingly prolactin concentrations (around 40 days PP) are higher in the high producers versus low producers (9).

Based on the described prior art it has been an object of the present invention to provide a medicament for a treatment of fertility problems in animal species, especially in cows which is, in the first place very effective and specific in its action and shows less side effects than the medicaments known in the art.

A further object of the present invention has been a method for the treatment of said fertility problems which is, due to the characterics of the medicament according to the present invention, less time consuming and which allows an easier application of said mediament.

This object has been achieved by administering a prolactin inhibitor to anovulatory animal species in the PP period.

Due to their specific effect, especially on the nervous system, alkaloids are a well known class of substances widely used in pharmacology. Examples for such alkaloids are, beside others, caffeine, morphine, strychnine, colchicine, and the socalled ergot alkaloids. Ergot (Claviceps purpurea) is a filamentous fungus growing on various types of grain, especially secale. Ergot alkaloids have been used in the past as labour stimulating and uterus contracting agents. Nowadays these substances are applied *inter alia* in cancer treatment. For example Biller et al. (6) used Cabergoline (Pharmacia, Columbus, OH), an ergotamine derivative specific for the D2 receptor, for the treatment of prolactinomas, the most commonly occuring pituarity tumour in men.

It has been surprisingly found now, that ergot alkaloids, e.g. Cabergoline, can be used as prolactin inhibitor in order to overcome fertility problems in the cow.

Example

All animals (n=6) except one were of the Swiss brown breed. The reminder was a Friesian Holstein. The ages varied between 3,5 and 5,5 years. At the commencement of the treatment 60 to 80 days had elapsed post partum without cycle (heat) or with unsuccessful Gestagen treatment (n=3). All animals were observed by the farmers and by the veterinarian (one initial and one intermediate and one control at the time of ovulation). As ovarian pathology acyclia was chosen. These animals are the most difficult to treat. Four cows exhibited true acyclia (no function on the ovary upon rectal palpation and one had a follicle (small) which had been controlled several times and found to be unchanged.

As Prolactin inhibitor Dostinex (Pharmacia & UpJohn/Cabergoline) (7) was chosen. The compound was pulverized and 2x10, 9, 8 and 3,5 mg were dissolved in 20 ml 0,9%-ige NaCl. The compound was administered into the uterus. Each catheter was rinsed with another 20 ml NaCl.

Results

No obvious side effects could be observed. All animals exhibited a drop in milk secretion by 30 to 40% when Cabergoline was administered AM. A drop in milk secretion was observed already in the evening. The drop lasted for 5 to 6 days. Ovulation occurred in all cows invariably approximately 2 weeks after treatment except the one who had a follicle on the ovary (3 days). Three animals developed a very pronounced standing heat as observed by the farmers. Two farmers apparently missed the heat. However occurrence of ovulation was substantiated by rectal palpation (ruptured follicle).

At the present already two cows have had their regular second cycle (in acyclia the first heat is usually afertile (lack of proceeding progesterone phase).

Conclusion

The drop in milk secretion proves 1) that the compound is biologically active in the cow over several days. This is in keeping with findings in human beings were the compound remains active as long as 7 days after administration (7) and 2) that despite the erroneous belief (10) Prolactin must be involved in milk production (immediate effect!)

The invariable and timewise consistent appearance of an ovulation is striking. It supports the belief that inappropriately elevated prolactin levels are the cause of PP anoestrus in the cow. Moreover since the compound was active in the most severe condition it would appear a powerful tool in combating this at the present most economically important condition.

Although only one cow had been tested with a low dose (3,5 mg) it appears that the individual dose can perhaps drastically be reduced.

Although the compound (for human use) is quite expensive it appears, given the large incidence of the problem, that the compound could be marketed at a reasonable, perhaps even high price for veterinary use due to its efficacy (single dose, causal treatment).

Larger scientific and clinical investigations are necessary to establish the efficacy of Cabergoline in lactational anoestrus. The application also would include repeat breeders. PP anoestrus also could be treated in other species such a sheep, horse and pig.

References

1) Mc Neilly, AS; Brit. med. Bull. 35, 151

2) Oxenreider et al., J. Anim. Sci. 33, 1026.**Jahr der Publik.?**

3) Stark, KDC; Schw. ARCM. Tiermeilk. 139, 8, 343

4) Grohn, YT; AM. J. Vet. Res. 55, No. 11, 1521

5) Lotthammer KH; Züchtungskunde 56 (6), 414 **(Jahr der Publ.?)**

6) Bartosik, D; Endocrinology 81, 186, 1967

7) Minagushi, H., Endocrinology 80, 603, 1967

8) Biller, B MK; J. Clin. Endocrinol. Metab. 81, 2338

9) Hart, IC; J. Endocr. 77, 333, 1978

10) Karg, H; Experientia 15.5, 1972.

Claims

1. Use of a prolactin inhibitor for the preparation of a medicament for a treatment of fertility problems in animal species.

2. Use according to claim 1 in which said prolactin inhibitor is an ergot alkaloid.

3. Use according to claim 2 in which said ergot alkaloid is an ergotamine derivative.

4. Use according to claim 3 in which said ergotamine derivative is Cabergoline.

5. Use according to any of the foregoing claims in which the animal species is a cow.

6. Method for a treatment of fertility problems in animal species by administering the prolactin inhibitor of claims 1 to 4.

7. Method accoding to claim 6, wherein said prolactin inhibitor is administered at an infusion or an injection site.

8. Method accoding to claim 7, wherein said prolactin inhibitor is administered into the uterus.

9. Method according to claim 8 wherein a catheter is used for administering the prolactin inhibitor into the uterus.

10. Method according to any of claims 7 to 9 wherein the prolactin inhibitor is administered in a dosis ranging from 3,5 to 10 mg per animal.

11. Method for a preparation of a medicament for the treatment of fertility problems in animal species wherein the prolactin inhibitor according to claims 1 to 4 is dissolved in a sodium chloride solution.

12. Method according to claim 10, wherein 3,5 to 10 mg of the prolactin inhibitor is dissolved in a sodium chloride solution.

13. Method according to claim 12, wherein the concentration of the sodium solution ranges between 0,9% und 5%.

AMENDED CLAIMS

[received by the International Bureau on 13 July 2000 (13.07.00) ;
original claims 1-13 replaced by new claims 1-9 (2 pages)]

1. Use of a prolactin inhibitor for the preparation of a medicament for a treatment of fertility problems in animal species wherein the prolactin inhibitor is Cabergoline.

2. Use of a prolactin inhibitor according to claim 1 wherein the animal species is a cow.

3. Method for a treatment of fertility problems in animal species by administering the ergotamine derivative Cabergoline.

4. Method according to claim 3 wherein said Cabergoline is administered into the uterus or any other infusion or injection site..

5. Method according to claim 4 wherein a catheter is used for administering said Cabergoline into the uterus.

6. Method according to any of claims 3-5, wherein said Cabergoline is administered in a dosis ranging from 3,5 to 10 mg per animal.

7. Method according to any of claims 3 to 6 wherin said Cabergoline is dissolved in a sodium chloride solution.

8. Method according to claim 7 wherein 3,5 to 10 mg of the inhibtor is dissolved in a sodium chloride solution.

9. Method according to claim 9, wherein the concentration of the sodium chloride solution ranges between 0,9% and 5%.

INTERNATIONAL SEARCH REPORT

International Application No
PC., IB 99/00448

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/48

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	EP 0 781 774 A (TAKEDA CHEMICAL INDUSTRIES LTD.) 2 July 1997 (1997-07-02) claims 1-14 page 69, line 29 -page 70, line 13 page 70, line 43 - line 48 ---	1,5-13
X	EP 0 003 286 A (SANDOZ AG) 8 August 1979 (1979-08-08) claims 1-10 page 5, line 17 -page 7, line 6 ---	1-3,6-13
X	EP 0 003 667 A (LILLY CO ELI) 22 August 1979 (1979-08-22) claims 1-4,6-9 page 58, line 1 - line 4 ---	1,2,6-10

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

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1999	12/11/1999

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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	FR 2 336 135 A (SANDOZ SA) 22 July 1977 (1977-07-22) claims 1-4,6-11 page 9, line 32 -page 10, line 24 page 11, line 23 -page 12, line 8	1-3,6,7, 10
X	GB 2 173 699 A (POLI IND CHIMICA SPA) 22 October 1986 (1986-10-22) the whole document	1-3,6,7, 10
X	US 4 054 660 A (CLEMENS JAMES A ET AL) 18 October 1977 (1977-10-18) claims 1,2 column 8, line 53 -column 9, line 12	1-3,6,7
X	US 3 985 752 A (KORNFELD EDMUND C ET AL) 12 October 1976 (1976-10-12) claims 1-7 column 5, line 7 - line 34	1-3,6,7
X	US 3 959 288 A (BACH NICHOLAS J ET AL) 25 May 1976 (1976-05-25) claims 1-8 column 5, line 59 -column 6, line 26	1-3,6,7, 10,11

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/00448

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.: 6-10
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 6-10 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:

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.

INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
PC., IB 99/00448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 781774 A	02-07-1997	CA 2192283 A	09-06-1997
		JP 9216823 A	19-08-1997
EP 0003286 A	08-08-1979	AT 373896 B	27-02-1984
		AT 39679 A	15-07-1983
		AU 525818 B	02-12-1982
		AU 4344479 A	26-07-1979
		CA 1122207 A	20-04-1982
		DK 12879 A,B,	21-07-1979
		ES 476972 A	16-06-1979
		FI 790091 A,B,	21-07-1979
		IE 48176 B	17-10-1984
		IL 56457 A	28-02-1982
		IT 1117205 B	17-02-1986
		JP 54122298 A	21-09-1979
		NZ 189422 A	15-12-1981
		PH 18155 A	03-04-1985
		PT 69097 A	01-02-1979
		US 4609657 A	02-09-1986
		ZA 7900225 A	27-08-1980
EP 0003667 A	22-08-1979	US 4166182 A	28-08-1979
		AR 228341 A	28-02-1983
		AT 371817 B	10-08-1983
		AT 91479 A	15-12-1982
		AT 385987 B	10-06-1988
		AT 554181 A	15-11-1987
		AT 385988 B	10-06-1988
		AT 554281 A	15-11-1987
		AU 523172 B	15-07-1982
		AU 4391779 A	16-08-1979
		BE 873883 A	02-08-1979
		BG 30474 A	15-06-1981
		CA 1114368 A	15-12-1981
		CH 639088 A	31-10-1983
		CS 203951 B	31-03-1981
		DD 141928 A	28-05-1980
		DK 51379 A,B,	18-09-1979
		EG 14076 A	31-12-1983
		ES 477547 A	16-04-1980
		FI 790351 A,B,	09-08-1979
		FR 2416891 A	07-09-1979
		GB 2014140 A,B	22-08-1979
		GR 72776 A	05-12-1983
		HK 43887 A	12-06-1987
		IE 47827 B	27-06-1984
		IL 56581 A	31-05-1982
		JP 1513267 C	24-08-1989
		JP 54115400 A	07-09-1979
		JP 63063544 B	07-12-1988
		JP 1063519 A	09-03-1989
		JP 1617634 C	12-09-1991
		JP 2040044 B	10-09-1990
		JP 1063520 A	09-03-1989
		JP 1619229 C	30-09-1991
		JP 2040647 B	12-09-1990
		LU 80886 A	07-06-1979
		LU 88294 A	04-05-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/00448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0003667 A		MX 154867 A	23-12-1987
		MX 5995 E	18-09-1984
		MX 155049 A	22-01-1988
		MX 9203107 A	31-07-1992
		MY 59785 A	31-12-1985
		NZ 189561 A	15-12-1981
		PH 14903 A	29-01-1982
		PT 69172 A,B	01-03-1979
		RO 76889 A	30-08-1981
		RO 81856 A	01-06-1983
		RO 81857 A	01-06-1983
		SU 912045 A	07-03-1982
		US 4180582 A	25-12-1979
FR 2336135 A	22-07-1977	CH 620441 A	28-11-1980
		AT 947076 A	15-12-1981
		AU 514288 B	05-02-1981
		AU 2079376 A	29-06-1978
		CA 1092100 A	23-12-1980
		DE 2656344 A	07-07-1977
		DK 554179 A	21-12-1979
		DK 562376 A,B,	24-06-1977
		ES 454442 A	01-03-1978
		FI 763587 A	24-06-1977
		FI 812150 A,B,	08-07-1981
		FI 812151 A	08-07-1981
		GB 1567484 A	14-05-1980
		HK 3483 A	20-01-1983
		IE 44242 B	23-09-1981
		IL 51133 A	30-11-1981
		JP 1370634 C	25-03-1987
		JP 52078900 A	02-07-1977
		JP 61033031 B	31-07-1986
		MY 6084 A	31-12-1984
		NL 7614018 A	27-06-1977
		NZ 182934 A	18-12-1978
		PH 14035 A	12-12-1980
		PT 66006 A,B	01-01-1977
		SE 432253 B	26-03-1984
		SG 63382 G	09-09-1983
		US 4348391 A	07-09-1982
		AT 370102 B	10-03-1983
		AT 759479 A	15-07-1982
		AT 376221 B	25-10-1984
		AT 759579 A	15-03-1984
		BE 849745 A	22-06-1977
		SE 7614085 A	24-06-1977
		ZA 7607640 A	26-07-1978
GB 2173699 A	22-10-1986	IT 1215261 B	31-01-1990
		DE 3525388 A	09-10-1986
		FR 2579894 A	10-10-1986
		JP 61280430 A	11-12-1986
US 4054660 A	18-10-1977	NONE	
US 3985752 A	12-10-1976	AR 207664 A	22-10-1976
		AR 208104 A	30-11-1976

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC., IB 99/00448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3985752 A		AT 354647 B	25-01-1979
		AT 91778 A	15-06-1979
		AT 348141 B	25-01-1979
		AT 927875 A	15-06-1978
		AT 347050 B	11-12-1978
		AT 927975 A	15-04-1978
		AU 498226 B	22-02-1979
		AU 8718275 A	09-06-1977
		BE 836308 A	08-06-1976
		BG 33287 A	14-01-1983
		BG 33288 A	14-01-1983
		BG 33435 A	15-02-1983
		CA 1062252 A	11-09-1979
		CA 1062253 A	11-09-1979
		CH 619465 A	30-09-1980
		CH 617197 A	14-05-1980
		CS 200484 B	15-09-1980
		CS 200483 B	15-09-1980
		CS 199609 B	31-07-1980
		DD 123749 A	12-01-1977
		DD 123748 A	12-01-1977
		DE 2554000 A	16-06-1976
		DK 547575 A,B,	07-06-1976
		DK 547675 A	07-06-1976
		ES 443275 A	16-09-1977
		ES 443276 A	16-08-1977
		ES 457709 A	01-03-1978
		FR 2293203 A	02-07-1976
		GB 1526835 A	04-10-1978
		GR 60025 A	31-03-1978
		GR 60026 A	31-03-1978
		IE 42372 B	30-07-1980
		IL 48573 A	12-03-1979
		JP 1295581 C	26-12-1985
		JP 59210085 A	28-11-1984
		JP 60017795 B	07-05-1985
		JP 1268719 C	10-06-1985
		JP 51082300 A	19-07-1976
		JP 59046235 B	10-11-1984
		MX 3113 E	18-04-1980
		NL 7514058 A	09-06-1976
		PH 12630 A	05-07-1979
		RO 64281 A	15-07-1979
		RO 65456 A	15-01-1980
		SE 421422 B	21-12-1981
		SE 7513640 A	08-06-1976
		SE 421423 B	21-12-1981
		SE 7513641 A	08-06-1976
US 3959288 A	25-05-1976	NONE	