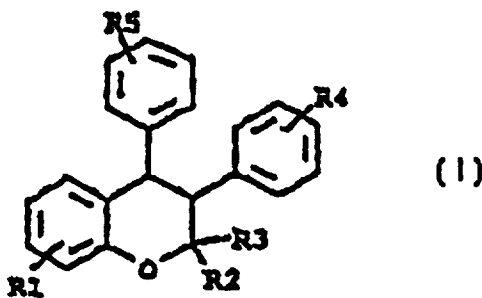




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/DK97/00302</p> <p>(22) International Filing Date: 7 July 1997 (07.07.97)</p> <p>(30) Priority Data: 0784/96 12 July 1996 (12.07.96) DK</p> <p>(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).</p> <p>(72) Inventor: GULDHAMMER, Birgitte Hjort; Elmegårdslé 71, DK-3400 Hillerød (DK).</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, GE, GH, HU, IL, 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, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	

(54) Title: USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR INHIBITING ONE OR MORE SYMPTOMS OF PREMENSTRUAL SYNDROME



(57) Abstract

The present invention provides novel uses of compounds of general formula (I) wherein R¹, R⁴ and R⁵ are individually hydrogen, hydroxy, halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or (tertiary amino)(C₁₋₆ alkoxy); and R² and R³ are individually hydrogen or C₁₋₆ alkyl, or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for inhibiting one or more symptoms of premenstrual syndrome.

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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for inhibiting one or more symptoms of premenstrual syndrome.

FIELD OF THIS INVENTION

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The present invention relates to the use of compounds of the general formula I for the inhibition of one or more symptoms of premenstrual syndrome. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

10

BACKGROUND OF THIS INVENTION

Premenstrual syndrome (PMS) is a common condition affecting a large proportion of women with normal functioning ovaries. The cause is still not known, but it seems to be related to the fluctuation of oestrogen and progesterone during the ovarian cycles. PMS is also referred to as late luteal phase syndrome (or late luteal phase dysphoric disorder).

The symptoms that occur can be both physical and psychological in nature. Irritability, snappiness and being on a "short fuse", depression and aggression are the most common reported psychological symptoms, but tension and anxiety are also frequent. Other psychological and behavioural symptoms which have been suggested to occur during the premenstrual phase and menstruation include, for example, decreased efficiency, insomnia, confusion, poorer judgement, difficulty in concentrating, crying, loneliness, restlessness, irritability, and mood swings. The effect of these symptoms can be compounded by physical symptoms which vary widely. The most common reported symptoms are tiredness, a feeling of abdominal bloating and breast swelling, and weight gain. Other symptoms which have been suggested to occur include, for example, dizziness, faintness, cold sweats, nausea, vomiting, hot flashes, muscle stiffness, headache, cramps, backache, general aches and pains, and water retention including, for example, weight gain, skin disorders, painful breasts, and swelling.

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Numerous treatments have been suggested for alleviating or minimising symptoms of premenstrual syndrome. These include, for example, non-pharmaceutical therapy such as variation in total energy intake and consumption of protein, fat, carbohydrates, vitamin B₆ and E, as well as e.g. supplements of magnesium or calcium and Evening primrose oil containing gamolenic acid. Other treatments include non-hormonal therapy such as treatment with

serotonin re-uptake inhibitors and hormonal therapy such as treatment with progesterone and progestogens, combined oral contraceptives, oestrogen replacement therapy, danazol and gonadotrophin hormone agonists. [See, e.g., Drug therapy in reproductive endocrinology, edited by Jean Ginsburg, Chapter 7 entitled "Premenstrual syndrome" by Abukhalil, I.E.H., *et al.*: 107-115].

Although a variety of treatment options are available, a multitude of women continue to suffer from premenstrual syndrome on a monthly basis. Accordingly, the present invention provides methods for alleviating one or more menstrual symptoms in women associated with premenstrual syndrome, and compositions therefore.

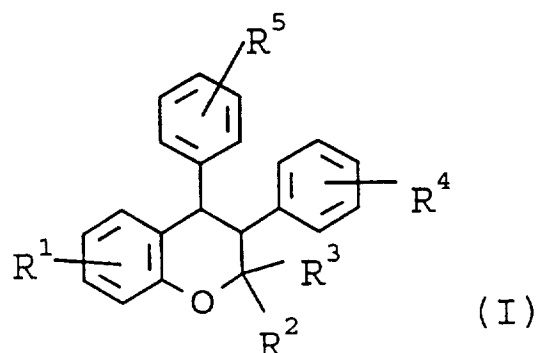
Centchroman is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman *et al.*, U.S. Patent Specification No. 4,447,622; Singh *et al.*, *Acta Endocrinol (Copenh)* **126** (1992), 444 - 450; Grubb, *Curr Opin Obstet Gynecol* **3** (1991), 491 - 495; Sankaran *et al.*, *Contraception* **9** (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra *et al.*, *Int J Cancer* **43** (1989), 781 - 783). Recently, centchroman as a racemate has been found as a potent cholesterol lowering pharmaceutical expressed by a significant decrease of the serum concentrations (S.D. Bain *et al.*, *J Min Bon Res* **9** (1994), S 394).

U.S. Patent No. 5,453,442 describes methods of lowering serum cholesterol and inhibiting smoother muscle cell proliferation in humans and inhibiting uterine fibroid disease and endometriosis in women by administering compounds of formula I as shown therein. Furthermore, US Patent No. 5,280,040 describes methods and pharmaceutical compositions for reducing bone loss using 3,4-diaryl chromans and their pharmaceutically acceptable salts. There is no disclosure in the patents of using the compounds to treat or alleviate premenstrual syndrome.

One object of the present invention is to provide compounds which can be used in alleviating one or more of the symptoms associated with premenstrual syndrome.

BRIEF DESCRIPTION OF THIS INVENTION

The present invention provides the use of compounds of the general formula I



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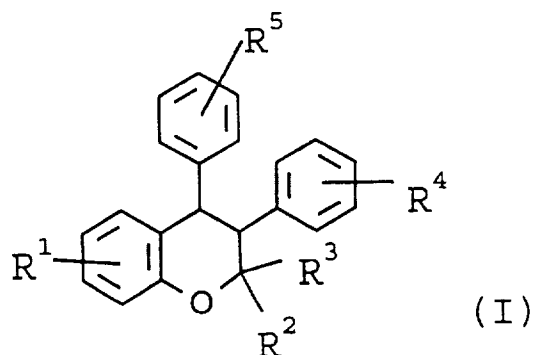
wherein R¹, R⁴ and R⁵ are individually hydrogen, hydroxy, halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or (tertiary amino)(C₁₋₆ alkoxy); and R² and R³ are individually hydrogen or C₁₋₆ alkyl, or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for inhibiting one or more symptoms of premenstrual syndrome.

10

DETAILED DESCRIPTION OF THIS INVENTION

The present invention is based on the discovery that a group of 3,4-diarylchromans of formula I are useful for alleviating one or more of the symptoms associated with premenstrual syndrome. Thus, the present invention provides the use of a compound of the general formula I

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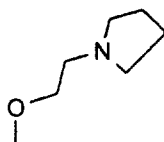
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wherein R¹, R⁴ and R⁵ are individually hydrogen, hydroxy, halogen, trifluoromethyl, lower alkyl, lower alkoxy or (tertiary amino)(lower alkoxy); and R² and R³ are individually hydrogen or

lower alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment of premenstrual syndrome. Thus, the present invention provides a method of inhibiting one or more symptoms of premenstrual syndrome comprising administering to a
5 subject in need of treatment an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. The term "inhibit" is defined to include its generally accepted meaning which includes, for example, prophylactically treating a female human subject from incurring the symptoms of PMS, holding in check each symptom, alleviating one or more symptoms and/or treating existing symptoms. As such, the present method includes
10 both medical treatment and /or prophylactic treatment, as appropriate.

Within the present invention, compounds of formula I as stated in claim 1 are used for inhibiting one or more symptoms of premenstrual syndrome in a patient. Within formula I, R^1 , R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino)(C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or a C_{1-6}
15 alkyl. As used herein, the term "lower alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term "lower alkoxy" includes straight and branched chain alkoxy radicals containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-
20 amyloxy, sec-amylloxy, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo. Herein, the term "(tertiary amino)(lower alkoxy)" is a lower alkoxy group which is substituted by a tertiary amino radical. The tertiary amino radical may be a N,N-dialkylamine such as a N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino and N,N-dibutylamino or a polymethyleneimine, e.g., piperidine, pyrrolidine,
25 N-methylpiperazine or morpholine. Preferred compounds include those in which R^1 is lower alkoxy; R^2 and R^3 are lower alkyl, especially methyl; R^4 is hydrogen; and R^5 is (tertiary amino)(lower alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R^1 is in the 7-position and is lower alkoxy, particularly methoxy; each of R^2 and R^3 is methyl, R^4 is hydrogen, and R^5 is in the 4-position and is a (tertiary amino)(lower alk-
30 oxy) radical such as 2-(pyrrolidin-1-yl)ethoxy. Preferred compounds include those in which R^1 is C_{1-6} alkoxy; R^2 and R^3 are C_{1-6} alkyl, especially methyl; R^4 is hydrogen; and R^5 is (tertiary amino)(C_{1-6} alkoxy) of the polymethyleneimine type. Within particularly preferred

embodiments, R¹ is in the 7-position and is C₁₋₆ alkoxy, particularly methoxy; each of R² and R³ is methyl, R⁴ is hydrogen, and R⁵ is in the 4-position and is a (tertiary amino)(C₁₋₆ alkoxy) radical such as 2-(pyrrolidin-1-yl)ethoxy with formula II



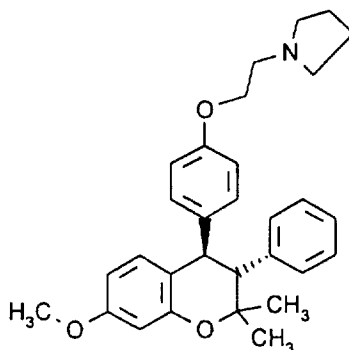
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(II)

10 To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

It is preferred to use the compounds of formula I in the transconfiguration. These compounds may be used as racemic mixtures, or the isolated d- or l- enantiomers may be used. The trans-l-enantiomers are more preferred.

15 A particularly preferred compound for use within the present invention is centchroman having the formula IV



as stated in claim 11.

20 Although only one enantiomer is shown, it will be understood that the formula IV is used herein to designate the transconfiguration of the 3- and 4-phenyl groups and that both the d- and l-enantiomers, as well as the racemic mixture, are included.

3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent Specification No. 3,340,276 to Carney *et al.*, U.S. Patent Specification No. 3,822,287 to Bolger, and Ray *et al.*, J Med Chem **19** (1976), 276 - 279, the contents of
25 which are incorporated herein by reference. Conversion of the cis isomer to the trans con-

figuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent Specification No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman *et al.* in U.S. Patent Specification No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. If R^2 is different from R^3 and R^4 is different from R^5 , the general formula I covers 8 optical isomers.

Within the present invention, 3,4-diarylchromans of formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, maleic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. A preferable salt is the hydrogen fumarate salt.

3,4-diarylchromans of formula I and their salts are useful within human and veterinary medicine, for example, in the treatment of patients suffering from premenstrual syndrome. For use within the present invention, 3,4-diarylchromans of formula I and their pharmaceutically acceptable salts are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or transdermal administration according to conventional methods. Formulations may further include one or more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc. One skilled in this art may formulate the compounds of formula I in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Genaro, ed., Mack Publishing Co., Easton, PA, 1990.

The present invention further provides a pharmaceutical composition for alleviating one or more of the symptoms of premenstrual syndrome comprising a compound of formula I and at least one pharmaceutical agent selected from the group consisting of an analgesic, a diuretic, and an antihistamine, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

Oral administration is preferred. Thus, the active compound of formula I is prepared in a form suitable for oral administration, such as a tablet or capsule. Typically, a pharmaceutically acceptable salt of the compound of formula I is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

Pharmaceutical compositions containing a compound of formula I may be administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount that provides a clinically significant effect against premenstrual syndrome. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art. A typical daily dose will contain a non-toxic dosage range of from about 0.001 to about 75 mg/kg patient per day of a compound of the present invention, preferably in a range from about 0.01 to 75, more preferably in the range from about 0.01 to 50 mg/kg patient per day.

The pharmaceutical compositions containing a compound of formula I may be administered in unit dosage form one or more times per day or week. In the alternative, they may be provided as controlled release formulations suitable for dermal implantation. Implants are formulated to provide release of active compound over the desired period of time, which can be up to several years. Controlled-release formulations are disclosed by, for example, Sanders *et al.*, J Pharm Sci 73 (1964), 1294 - 1297, 1984; U.S. Patent Specification No. 4,489,056; and U.S. Patent Specification No. 4,210,644, which are incorporated herein by reference.

The following examples are offered by way of illustration, not limitation.

Examples of preferred compounds of formula I are centchroman as a racemic mixture and as isolated l-centchroman and d-centchroman enantiomers. Furthermore, 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman is a preferred compound. The more preferred compound is isolated l-centchroman (l-3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

Examples of pharmaceutically acceptable acid addition salts are salts with non-toxic acids, either inorganic acids such as hydrochloric acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, succinic acid, gluconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing the invention in diverse forms thereof.

5

Example

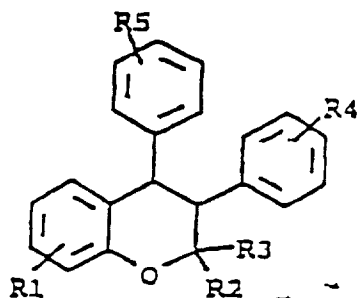
A clinical case-control study is performed in six to fifty women. The women are in good general health and have regular menstruation, but suffer from PMS as defined above. Symptoms are reported by questionnaires. The women are divided into two groups, a test group which receives the active compound of this invention, and a control group which receives a placebo. Women in the test group receives between 1 and 500 mg of the test compound orally per day for one to six months. Regularly throughout the study symptoms are carefully recorded and the effects on the symptoms associated with PMS are compared both between the groups and for each patient also with the symptoms reported before treatment began. Effects on any of the symptoms of PMS of the test compound are considered as positive.

CLAIMS

1. The use of compounds of the general formula I

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wherein R^1 , R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino)(C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for inhibiting one or more symptoms of premenstrual syndrome.

20

2. The use, according to claim 1, wherein R^1 in the compound used is C_{1-6} alkoxy, R^2 and R^3 are C_{1-6} alkyl, R^4 is hydrogen and R^5 is (tertiary amino) C_{1-6} alkoxy.

25

3. The use according to anyone of claims 1 or 2 wherein R^1 is methoxy.

4. The use according to anyone of claims 1-3 wherein R^2 is methyl.

5. The use according to anyone of claims 1-4 wherein R^3 is methyl.

30

6. The use according to anyone of claims 1-5 wherein R^4 is hydrogen.

7. The use according to anyone of claims 1-6 wherein R^5 is a group as stated in formula II below:

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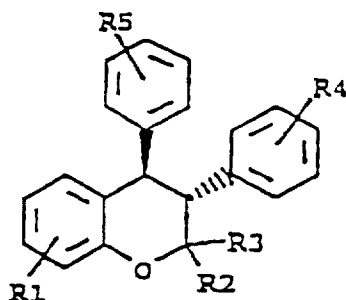


(II)

10 8. The use according to anyone of claims 1-7 wherein said compound is an isolated d- or l-enantiomer.

9. The use according to anyone of the preceding claims wherein said compound has the general formula III as stated below:

15



(III)

wherein R¹, R², R³, R⁴ and R⁵ each are as defined in above claim 1.

25 10. The use according to anyone of the preceding claims wherein said compound is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman.

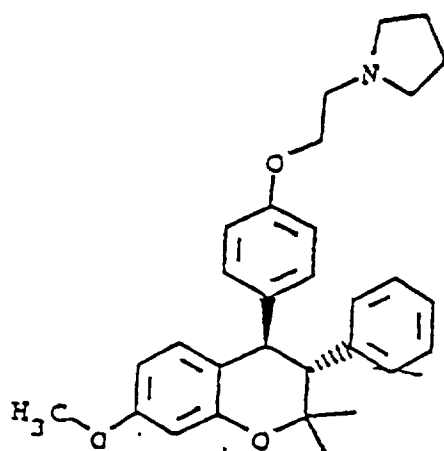
11. The use according to anyone of the preceding claims wherein said compound is an isolated l-enantiomer.

30

12. The use according to claim 1 wherein said compound is centchroman 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy]phenyl]-7-methoxychroman having the formula IV as stated below:

5

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(IV)

13. The use according to claim 12 wherein said compound is an isolated l-enantiomer of
15 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy]phenyl]-7-methoxychroman.

14. The use according to anyone of the preceding claims wherein said composition is in
a form suitable for oral administration.

20 15. The use according to anyone of the preceding claims wherein said compound is
administered as a dose in a range from about 0.001 to 75 mg/kg patient per day.

16. The use according to anyone of the preceding claims wherein said composition is
administered one or more times per day or week.

25

17. The use according to any one of the preceding claims wherein said composition is
in the form of a dermal implant.

18. Method of inhibiting one or more symptoms of premenstrual syndrome comprising
30 administering to a patient a clinically effective amount of a compound of above formula I
stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt
thereof in an amount sufficient to treat premenstrual syndrome.

19. A method of treating or preventing premenstrual syndrome which method comprises administering a clinically effective amount of compounds and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment.

5 20. Any novel feature or combination of features described herein.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00302

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 31/35
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)

IPC6: A61K

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

SE,DK,FI,NO classes as above

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

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Current Opinion in Endocrinology and Diabetes, Volume 2, 1995, Joseph F. Mortola, "Pathophysiology and treatment of premenstrual syndrome" page 483 - page 492 -- -----	1-17

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier document but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 1997	16 -10- 1997

Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00302

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.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy,
see rule 39.1.
2. Claims Nos.: 20
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:
Claim 20 is obscure and does not clearly define the matter for which protection is sought, see Article 6.
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.