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(54) Title: ESTROGENIC COMPONENT FOR TREATING DECREASED LIBIDO IN WOMEN

(57) Abstract: The present invention is concerned with a method of treating decreased libido in pre-menopausal women, said decreased libido being the result of the repeated administration of a progestogenic component, wherein the method comprises the administration of the estrogenic component to a woman in an effective amount to improve the woman's libido. The present method is particularly suited for treating decreased libido in women using hormonal contraceptives that employ administration of a progestogenic component.

ESTROGENIC COMPONENT FOR TREATING DECREASED LIBIDO IN WOMEN

TECHNICAL FIELD OF THE INVENTION

The present invention is concerned with a method of treating decreased libido in pre-menopausal women, said decreased libido being the result of the repeated administration of a progestogenic component, e.g. as part of an oral contraceptive protocol.

BACKGROUND OF THE INVENTION

The presence of a normal libido, defined as the urge to engage in sexual activity and intercourse, is an important component of an individual's well-being. Decreased libido is a common complaint in postmenopausal females. However, also pre-menopausal females may sometimes suffer from decreased libido.

This decrease in libido is characterised by a lack of interest in sexual intercourse and/or the lack of ability to achieve orgasm. A decrease in libido may also be accompanied by a decrease in intensity of orgasm. It is important to note that this decrease in libido is often associated with a profound sense of loss of a once normal and active interest in sexual activity.

US 5,439,931 (Sales) describes a method of increasing libido in post-menopausal women comprising administering to a female human an effective amount of a benzothiophene substance like raloxifene, a selective estrogen receptor modulator (SERM).

WO 00/66084 (Cole et al.) relates to aerosol formulations and devices for increasing libido in women via acute testosterone administration. It is stated in this application that in both men and women the primary naturally occurring hormone responsible for libido is testosterone.

SUMMARY OF THE INVENTION

The inventors have found that decreased libido in some pre-menopausal women is associated with the repeated administration of a progestogenic component, e.g. as part of a

contraceptive protocol. The inventors have additionally discovered that complaints about decreased libido in women who use a hormonal contraceptive, are strongly correlated with reduced, i.e. sub-physiological serum estrogen levels. The administration of an estrogen component in an effective amount to significantly increase the woman's estrogen activity was found to be a very effective way to improve or restore libido in such women.

DETAILED DESCRIPTION OF THE INVENTION

Consequently, the present invention is specifically concerned with a method of treating decreased libido in pre-menopausal women, said decreased libido being the result of the repeated administration of a progestogenic component, wherein the method comprises the administration of the estrogenic component to a woman in an effective amount to improve the woman's libido.

Throughout this document the term "progestogenic component" is used to describe substances that are capable of binding to the one or more progesterone receptors and that can activate said receptors. Similarly, the term "estrogenic component" is used to refer to substances that are capable of binding to one or more estrogen receptors and that can activate one or more of these receptors.

As mentioned herein before, the decreased libido as a result of repeated administration of a progestogenic component is believed to be caused by a relative estrogen deficiency. The administration of progestogenic components is known to suppress the pituitary release of luteinising hormone (LH) and follicle stimulating hormone (FSH) which suppression in turn will lead to a reduction of the endogenous production of the estrogen 17ß-estradiol. Without the co-administration of a sufficient amount of an estrogen, the repeated administration of a progestogenic component may lead to a significant reduction of the serum estrogen level and may even induce hypoestrogenism.

Despite the fact that most oral contraceptives employ a combination of a progestogenic component and an estrogen, the inventors have unexpectedly found that in some cases the amount of estrogen that is co-administered is insufficient to maintain libido. Consequently, the present method is particularly suited for treating decreased libido in women using hormonal contraceptives that employ combined administration of a progestogenic component and an estrogen, in particular once daily oral administration of the combination of these components. Decreased libido occurs most frequently in females using a contraceptive

that employs a progestogenic component *per se,* or alternatively a progestogenic component in combination with a relatively low amount of an estrogen. In the context of a hormonal contraceptive, by a relatively low amount of an estrogen is meant an amount which is equivalent to a daily oral dosage of at most 35 μg ethinyl estradiol. The present method is particularly advantageous in case the estrogen in the contraceptive is administered in an amount which is equivalent to a daily oral dosage of at most 25 μg ethinyl estradiol, preferably of at most 20 μg ethinyl estradiol. Most preferably, the present method is used to treat decreased libido resulting from daily oral administration of a progestogenic component in combination with an estrogen in a daily amount which is equivalent to between 5 and 25 μg ethinyl estradiol.

Although, in accordance with the present method, it may be advantageous to co-administer other active principles together with the estrogenic component it is preferred not to co-administer a progestogenic component.

The administration of the estrogenic component is particularly effective if the period during which the estrogenic component is administered coincides with the period during which a progestogenic component is administered. Whereas, in the context of contraceptive methods, the administration of the progestogenic component occurs at regular intervals, the present method does not require the administration of the estrogenic component to follow a predefined pattern. As a matter of fact, it is deemed advantageous to leave the decision as to when to administer the estrogenic component to the woman, meaning that the woman can decide when to stimulate her libido. Consequently, in the present method, it is preferred that the libido improving administration of the estrogenic component and the repeatedly administered progestogenic component are done separately and at different intervals. In other words, it is preferred that the estrogenic component and progestogenic component are administered according to different protocols.

Examples of estrogenic components that may suitably be used in the present invention include ethinyl estradiol, mestranol, quinestranol, estradiol, estrone, estran, estriol, conjugated equine estrogens, precursors capable of liberating such an estrogenic component when used in the present method and mixtures thereof. Preferably the estrogenic component is selected from the group consisting of ethinyl estradiol, estradiol, precursors capable of liberating such an estrogenic component when used in the present method and mixtures thereof. More preferably the estrogenic component is selected from the group consisting of ethinyl estradiol, 17β-estradiol and mixtures thereof. Most preferably the estrogenic component is ethinyl estradiol.

Typically, in the present method, the estrogenic component is administered in a dosage which is equivalent to an oral dosage of between 5 and 40 μg ethinyl estradiol, preferably of between 10 and 30 μg ethinyl estradiol. In case of 17β-estradiol an oral dosage of between 0.5 and 4 mg is equivalent to an oral dosage of between 5 and 40 μg ethinyl estradiol The term "dosage" as used herein refers to the amount that is administered within a relatively short time interval, e.g. of less than 10 minutes, preferably of less than 5 minutes. The term dosage also encompasses the action of applying a dosage unit which, following said application, will effectively introduce the estrogenic component into the body over a prolonged period of time, as is the case for e.g. transdermal or intravaginal administration. If the actual release of the estrogenic component from such a sustained release dosage unit continuous for more than 24 hours, the aforementioned dosage amounts are to be calculated on a daily basis. A dosage may be administered in the form of a single dosage unit, or alternatively in the form of 2 or more dosage units, provided these 2 or more dosage units are administered within the aforementioned short interval. Generally, in the present method, the estrogenic component will be administered at intervals that exceed 12 hours. Preferably the interval between subsequent administrations of the estrogenic component exceeds 20 hours.

In another preferred embodiment the estrogenic component is a selective estrogen receptor modulator (SERM). Examples of SERMS that may suitably be employed in the present method include tamoxifen, Z-tamoxifen, raloxifene, toremifene, idoxifene, droloxifene, nafoxidine, trioxifene, MER-25, EM-652, clomiphene, cyclophenil, lasofoxifene, arzoxifene, levormeloxifene, zindoxifene, miproxifene, fulvestrant, LY-117018, LY-326315ZK119010 LY-357489, GW-5638, GW 7603, GW-7604, TSE-424, FC1271a, Sch-57050, CDRI-85-287, NNC-45-0095, SG-292, RU-51625, RU-58668, ZK-164015, BE-14348B, MDL-104931, MDL-104890, MDL-103323, R-1128B, RU-45144, RU-39411, WS-7528, NV-50, precursor of these substances and combination of any of these compounds. Administration of estrogens has been associated with endometrial proliferation in women and it is a widely held belief that "unopposed" estrogen therapy may increase the risk of endometrial cancer (Cushing et al., 1998. Obstet. Gynecol.91, 35-39; Tavani et al., 1999. Drugs Aging, 14, 347-357). The administration of a SERM does not suffer from this drawback.

The present method is particularly suited for treating decreased libido in women using a hormonal contraceptive, in particular females who are repeatedly (self) administering a progestogenic component, optionally in combination with an estrogen, in accordance with a contraceptive protocol. .

In a particularly preferred embodiment of the invention the present method employs the co-administration of the estrogenic component with an androgenic component. It was found that in some cases the combined administration of an estrogenic and an androgenic component is more effective than the administration of the estrogenic component *per se* in achieving improved libido. The androgenic component may suitably be selected from the group consisting of dehydroepiandrosterone (DHEA); DHEA-sulphate; testosterone; testosterone esters such as testosterone undecanoate , testosterone propionate, testosterone phenylpropionate, testosterone isohexanoate, testosterone enantate, testosterone bucanate, testosterone decanoate, testosterone buciclate; danazol; gestrinone; methyltestosterone; mesterolon; stanozolol; androstenedione; dihydrotestosterone; androstanediol; metenolon; fluoxymesterone; oxymesterone; methandrostenolol; MENT; precursors capable of liberating these androgens when used in the present method and mixtures thereof. More preferably the androgenic component is selected from the group consisting of DHEA, testosterone esters, androstenedione, precursors capable of liberating these androgens when used in the present method and mixtures thereof. Most preferably the androgenic component is selected from the group consisting of dehydroepiandrosterone, esters of testosterone and mixtures thereof.

Preferably the testosterone esters employed in the present method comprise an acyl group which comprises at least 6, more preferably from 8-20 and preferably 9-13 carbon atoms. Most preferably the androgens used in the present method are DHEA and/or testosterone undecanoate. These androgens offer the advantage that they can effectively be used in oral dosage units.

It is noted that, for instance, DHEA, testosterone undecanoate and androstenedione are precursors of testosterone and that said precursors *per se* exhibit virtually no affinity for androgen receptors in the female body. The effectiveness of the androgens within the method of the invention is determined by their functionally active form, which may well be different from the form in which they are administered.

In the present method the androgen is preferably provided in an amount equivalent to an oral dosage of at least 5 mg DHEA, which is equivalent to an oral dosage of at least 1 mg testosterone undecanoate. More preferably the androgen is provided in an amount which is equivalent to an oral dosage of a least 10 mg DHEA, most preferably of at least 20 mg DHEA. Usually the androgen dosage employed will not exceed the equivalent of an oral dosage of 250 mg DHEA, which is equivalent to an oral dosage of 50 mg testosterone undecanoate. Preferably the androgen is administered in a dosage which does not exceed the

equivalent of an oral dosage of 120 mg DHEA, more preferably it does not exceed the equivalent of an oral dosage 60 mg DHEA.

In the present method, the estrogenic component, and the optional androgenic component, may suitably be administered orally, pulmonary, parenterally, sublingually, transdermally, intravaginally, intranasally or buccally. In a preferred embodiment the estrogenic component, and the optional androgenic component, are administered orally, pulmonary or intranasally. Most preferably the estrogenic component is administered orally. In case the present method employs a combination of an estrogenic and an androgenic component, both components are advantageously delivered by means of the same mode of administration. Most preferably both components are administered orally, preferably in the form of a single oral dosage unit that contains both the estrogenic and the androgenic component.

In the prior art it has been suggested that DHEA may have a beneficial effect on libido in females who suffer from adrenal sufficiency. In a preferred embodiment the present method does not encompass the treatment of a woman suffering from adrenal sufficiency.

The invention is further illustrated by means of the following examples.

EXAMPLES

Example 1

A clinical study is conducted in 40 healthy young women who have been using a low dose oral contraceptive (20 μg ethinyl estradiol in combination with a progestogen) for at least 3 years. In a baseline cycle, coitus frequency and sexual function are recorded.

Each participant receives blinded medication in 2 differently labeled bottles, filled with tablets. One bottle comprises tablets that contain 20 μg ethinyl estradiol, whilst the other bottle contains identical placebo tablets. The participants are allowed to choose from which bottle to take a tablet, but are instructed not to use more than 1 tablet per 24 hours and not more than 4 tablets a week. The total duration of the study is 4 months, during which period the participants continue with their usual low dose oral contraceptive regimen.

It is found that during the study participants use significantly more ethinyl estradiol containing tablets than placebo's. In addition, analysis of the data shows that women who mainly used ethinyl estradiol containing tablets report improved libido and sexual enjoyment in comparison to baseline. Consequently, it can be concluded that oral administration of 20 μg

ethinyl estradiol to users of a low dose oral contraceptive leads to an improvement of libido and sexual enjoyment in some of these users, whilst no undesirable side-effects are reported.

Example 2

Example 1 is repeated except that instead of tablets containing 20μg ethinyl estradiol, tablets containing 2 mg 17β-estradiol are used. The findings show that oral administration of 2 mg 17β-estradiol to users of a low dose oral contraceptive leads to an improvement of libido and sexual enjoyment in some of these users. Again no undesirable side-effects are reported.

CLAIMS

1. Use of an estrogenic component in the manufacture of a pharmaceutical composition for use in a method of treating decreased libido in a pre-menopausal woman, said decreased libido being the result of the repeated administration of a progestogenic component, wherein the method comprises the administration of the estrogenic component to the woman in an effective amount to improve the woman's libido.

2. Use according to claim 1, wherein the decreased libido is the result of daily oral administration of a progestogenic component, optionally in combination with an estrogen in a daily amount which is equivalent to at most 35 μg ethinyl estradiol, preferably at most 25 μg ethinyl estradiol.

3. Use according to claim 2, wherein the decreased libido is the result of daily oral administration of a progestogenic component in combination with an estrogen in a daily amount which is equivalent to between 5 and 25 μg ethinyl estradiol.

4. Use according to claim 1 or 2, wherein the estrogenic component is not co-administered with a progestogenic component.

5. Use according to any one of claims 1-3, wherein the period during which the estrogenic component is administered coincides with the period during which a progestogenic component is administered, but wherein the libido improving administration of the estrogenic component and the repeated administration of the progestogenic component are done separately and at different intervals.

6. Use according to any one of claims 1-4, wherein the progestogenic component is administered in accordance with a contraceptive protocol.

7. Use according to any one of claims 1-5, wherein the estrogenic component is administered in a dosage which is equivalent to an oral dosage of between 5 and 40 μg ethinyl estradiol, preferably of between 10 and 30 μg ethinyl estradiol.

8. Use according to any one of claims 1-6, wherein the estrogenic component is selected from the group consisting of estrogens, selective estrogen receptor modulators (SERMs) and combinations thereof.

9. Use according to claim 8, wherein the estrogenic component is selected from the group consisting of ethinyl estradiol, mestranol, quinestranol, estradiol, estrone, estran, estriol, conjugated equine estrogens, tamoxifen, Z-tamoxifen, raloxifene, toremifene, idoxifene, droloxifene, nafoxidine, trioxifene, MER-25, EM-652, clomiphene, cyclophenil, lasofoxifene, arzoxifene, levormeloxifene, zindoxifene, miproxifene, fulvestrant, LY-117018, LY-326315ZK119010 LY-357489, GW-5638, GW 7603, GW-7604, TSE-424, FC1271a, Sch-57050, CDRI-85-287, NNC-45-0095, SG-292, RU-51625, RU-58668, ZK-164015, BE-14348B, MDL-104931, MDL-104890, MDL-103323, R-1128B, RU-45144, RU-39411, WS-7528, NV-50, precursor of these substances and combination of any of these compounds. precursors capable of liberating such an estrogenic component when used in the present method and mixtures thereof.

10. Use according to claim 9, wherein the estrogenic component is selected from the group consisting of ethinyl estradiol, estradiol, precursors capable of liberating such an estrogenic component when used in the present method and mixtures thereof.

11. Use according to any one of claims 1-10, wherein the estrogenic component is co-administered with an androgenic component.

12. Use according to any one of claims 1-11, wherein the estrogenic component is administered orally, pulmonary, parenterally, sublingually, transdermally, intravaginally, intranasally or buccally.

13. Use according to claim 12, wherein the estrogenic component is administered orally, pulmonary or intranasally.

14. Use according to any one of claims 1-13, wherein the woman does not suffer from adrenal insufficiency.

INTERNATIONAL SEARCH REPORT

PCT/NL 03/00125

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565 A61K31/567 A61K31/566 A61K31/38 A61P15/12
A61K31/4453 A61K31/4535 A61K31/4025 A61K31/00

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 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, PAJ, BIOSIS, MEDLINE, PASCAL, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 659 411 B (LILLY CO ELI) 28 June 1995 (1995-06-28) page 2, line 3 -page 3, column 27; claims 1-4; example 2	1-14
X	WO 99 63973 A (ENDORECHERCHE INC) 16 December 1999 (1999-12-16) page 5, line 3-20 page 29, line 28 -column 31, line 16; claims 10-14,21-24	1-14
X	US 5 872 114 A (LABRIE FERNAND) 16 February 1999 (1999-02-16) column 7, line 6-65 column 14, line 12-44 column 19, line 55-67 column 22, line 34 -column 23, line 24; claims 1-8	1-14

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

[X] 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	Date of mailing of the international search report
23 May 2003	06/06/2003

Name and mailing address of the ISA	Authorized officer
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	Trifilieff-Riolo, S

Form PCT/ISA/210 (second sheet) (July 1992)

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 5 854 229 A (LABRIE FERNAND) 29 December 1998 (1998-12-29) column 7, line 6-67; claims 1-4 column 19, last paragraph column 14, line 14-33	1-14
X	E-E BAULIEU ET AL: "Dehydroepiandrosterone (DHEA), DHEA sulfate and aging: Contribution of the DHEAge study to a sociobiomedical issue" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 8, 11 April 2000 (2000-04-11), pages 4279-4284, XP002141516 ISSN: 0027-8424 abstract page 4283, left-hand column, last paragraph -right-hand column, paragraph F	1-14
X	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 2000 ALDRIGHI J M ET AL: "Climaterium" Database accession no. EMB-2001044380 XP002241812 abstract & REVISTA BRASILEIRA DE MEDICINA 2000 BRAZIL, vol. 57, no. SPEC.ISS., 2000, pages 209-215, XP009011185 ISSN: 0034-7264	1-14
X	WO 98 33499 A (NOVONORDISK AS) 6 August 1998 (1998-08-06) page 3, line 22 - line 26 page 5, line 15 - line 19	1-14
X	WO 99 00019 A (MACDONALD BRIAN R ;SMITHKLINE BEECHAM CORP (US)) 7 January 1999 (1999-01-07) page 2, line 27 - line 28 page 3, line 5 - line 10 page 3, line 21	1-14
A	US 5 661 141 A (PETROW VLADIMIR) 26 August 1997 (1997-08-26) column 1, line 39-50	1-14

INTERNATIONAL SEARCH REPORT

PCT/NL 03/00125

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:

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 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:

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

Claims 1 to 8 and 10 to 14 relate to the use of a compound defined by reference to a desirable characteristic, namely "an estrogenic compound", i.e. a compound capable of binding to estrogen receptor(s) and that can activate one or more of these receptor(s).

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or 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 compound 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 claim 9.

The same remark applies to claim 11 which refers to "an androgenic component".

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.

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