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Use of estradiol valerate or 17β -estradiol in combination with dienogest for oral therapy for maintaining and/or increasing the female libido

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Field of the invention



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The invention relates to the use of estradiol valerate or 17β -estradiol (estradiol) in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest) in a multiphase or single-phase combination product for oral therapy for maintaining and/or increasing female libido, where appropriate also united with oral contraception.

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The total number of daily dose units of the multiphase combination and of one of the pharmaceutically acceptable placebo or of the single-phase combination and, where appropriate, the pharmaceutically acceptable placebo-containing or the placebo- and hormone-free daily dose units correspond to 28 daily dose units.

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Prior art

Female libido is a very complex event which is influenced by numerous hormonal and psychosocial factors. It has long been known that the onset of the menopause may be accompanied by a decrease in sexual desire in women. Reasons being discussed in this context are the decreasing level of endogenous estradiol and the reduced androgen level. Less known is the fact that intake of conventional combined oral contraceptives and progestin-only pills (POPs) may lead to an acquired loss of/decrease in libido. Disorders of this kind are subsumed under the term "acquired OC-associated hypoactive sexual desire disorder (HSDD)". (Blitzer: Kontrazeption und Sexualität, Therapeutische

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Umschau, Vol. 51, 1994, edition 2, 110-114). The cause of this is not clear, various theses are being discussed. It has to date not been possible to prevent this observed phenomenon sufficiently. (Sex steroids
5 and libido, The European Journal of Contraception and reproductive Health care (1997 - 253-258).

Disclosure of the invention

10 The invention is based on the object of finding a means for maintaining and/or increasing female libido.

The object is achieved according to the invention through the use of estradiol valerate or estradiol in
15 combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3one (dienogest) for producing a multiphase combination product or single-phase combination product for oral therapy for maintaining and/or increasing female libido.

20 It has been found, surprisingly, that oral contraception occurs concomitantly with the maintenance of and/or the increase in female libido.

25 Advantageously, estradiol valerate or estradiol is employed in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3one (dienogest), comprising a first phase of 2 daily dose units of 3 mg of estradiol valerate or of an equivalent dose of estradiol (less
30 than 3 mg), a second phase of 2 groups of daily dose units, where the first group comprises 5 daily dose units of a combination of 2 mg of estradiol valerate or of an equivalent dose of estradiol (less than 2 mg) and 2 mg of dienogest, and the second group comprises
35 17 daily dose units of a combination of 2 mg of estradiol valerate or of an equivalent dose of estradiol (less than 2 mg) and 3 mg of dienogest, a

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- third phase of 2 daily dose units with 1 mg of estradiol valerate or an equivalent dose of estradiol (less than 1 mg) and a further phase of 2 daily dose units of pharmaceutically acceptable placebo for
5 producing a multiphase combination product having a total number of 28, for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception.
- 10 Advantageously, also estradiol valerate or estradiol is employed in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest), comprising a first phase of 2 daily dose units of 3 mg of estradiol
15 valerate or of an equivalent dose of estradiol (less than 3 mg), a second phase of 2 groups of daily dose units, where the first group comprises 5 daily dose units of a combination of 2 mg of estradiol valerate or of an equivalent dose of estradiol (less than 2 mg) and 3 mg of dienogest, and the second group comprises
20 17 daily dose units of a combination of 2 mg of estradiol valerate or of an equivalent dose of estradiol (less than 2 mg) and 4 mg of dienogest, a third phase of 2 daily dose units with 1 mg of estradiol valerate or an equivalent dose of estradiol
25 (less than 1 mg) and a further phase of 2 daily dose units of pharmaceutically acceptable placebo for producing a multiphase combination product having a total number of 28, for oral therapy for maintaining and/or increasing female libido, where appropriate
30 united with oral contraception.

Also, advantageously, estradiol valerate or estradiol is employed in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest), comprising a
35 first phase of 2 daily dose units of 3 mg of estradiol valerate or of an equivalent dose of estradiol (less than 3 mg), a second phase of 2 groups of daily dose

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units, where the first group comprises 5 daily dose units of a combination of 2 mg of estradiol valerate or of an equivalent dose of estradiol (less than 2 mg) and 1 mg of dienogest, and the second group comprises 5 17 daily dose units of a combination of 2 mg of estradiol valerate or of an equivalent dose of estradiol (less than 2 mg) and 2 mg of dienogest, a third phase of 2 daily dose units with 1 mg of estradiol valerate or an equivalent dose of estradiol 10 (less than 1 mg) and a further phase of 2 daily dose units of pharmaceutically acceptable placebo for producing a multiphase combination product having a total number of 28, for oral therapy for maintaining and/or increasing female libido, where appropriate 15 united with oral contraception.

Advantageously, also, estradiol valerate or estradiol is employed in combination with 17 α -cyanomethyl-17- β -hydroxyestra-4,9-dien-3-one (dienogest), comprising a 20 first phase of 3 daily dose units of 3 mg of estradiol valerate or of an equivalent dose of estradiol (less than 3 mg), a second phase of 2 groups of daily dose units, where the first group comprises 4 daily dose units of a combination of 2 mg of estradiol valerate or 25 of an equivalent dose of estradiol (less than 2 mg) and 1 mg of dienogest, and the second group comprises 16 daily dose units of a combination of 2 mg of estradiol valerate or of an equivalent dose of estradiol (less than 2 mg) and 2 mg of dienogest, a 30 third phase of 2 daily dose units with 1 mg of estradiol valerate or an equivalent dose of estradiol (less than 1 mg) and a further phase of 3 daily dose units of pharmaceutically acceptable placebo for producing a multiphase combination product having a 35 total number of 28, for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception.

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Also, advantageously, less than or equal to 3 mg of estradiol valerate or estradiol are employed in combination with less than or equal to 2.00 mg of 17 α -cyanomethyl-17- β -hydroxyestra-4,9-dien-3one (dienogest) in a single-phase product for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception. The single-phase combination comprises 21, 22, 23, 24, 25, 26, 27 daily dose units with constant amount of dienogest and estradiol valerate or dienogest and estradiol, and 7, 6, 5, 4, 3, 2, 1 pharmaceutically acceptable placebo-containing or placebo- and hormone-free daily dose units, to give a total number of daily dose units corresponding to 28.

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It is likewise advantageous to administer the single-phase product in an extended cycle comprising

- a first phase of a single-phase preparation of 1.0-2.0 mg of dienogest and 10-30 μ g of ethinyl estradiol of n x 21 daily dose units with n = 2 to 5 and with constant amount of dienogest and estradiol
- a second phase following n = 2 to 5 of 7 pill-free daily dose units.

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It proves particularly advantageous to use the single-phase product with 21-27 daily dose units of dienogest, estradiol valerate or estradiol and 1 to 7 placebo- or hormone-free or consists of 1 to 7 placebo-containing daily dose units, so as to give a total number of daily dose units corresponding to 28, and thereafter in the above extended cycle.

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Investigations of the efficacy of the claimed formulation

Clinical trials with an orally administered multiphase combination of estradiol valerate and dienogest, in which the first phase consists of 2 daily dose units of 3 mg of estradiol valerate, the second phase of 2 groups of daily dose units. The first group of this second phase consists of 5 daily dose units of a combination of 2 mg of estradiol valerate and 2 mg of dienogest and the second group of 17 daily dose units of a combination of 2 mg of estradiol valerate and 3 mg of dienogest. The third phase comprises 2 daily dose units with 1 mg of estradiol valerate and a further phase consists of 2 daily dose units of pharmaceutically acceptable placebo. The total of days of an administration cycle of the multiphase combination and of the pharmaceutically acceptable placebo corresponds to 28 days.

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In a randomized, double-blind clinical trial, 800 women aged between 18 and 50 years (400 in the 18 to 35 years age group and 400 in the 36 to 50 years age group) and having given written informed consent to their participation in the trial were treated with 2 different treatments.

Treatment (A) corresponded to the combination mentioned. The second treatment (B) corresponded to Miranova (standard OC).

The study comprised a pre-treatment cycle, 7 treatment cycles and one after-treatment cycle (follow-up phase).

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Claims

1. Use of estradiol valerate or 17β -estradiol in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest), for producing a multiphase combination product or a single-phase combination product for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception.
2. Use of estradiol valerate or estradiol in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest) as claimed in claim 1, comprising a first phase of 2 daily dose units of 3 mg of estradiol valerate or of less than 3 mg of estradiol, a second phase of 2 groups of daily dose units, where the first group comprises 5 daily dose units of a combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 2 mg of dienogest and the second group comprises 17 daily dose units of a combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 3 mg of dienogest, a third phase of 2 daily dose units with 1 mg of estradiol valerate or less than 1 mg of estradiol and a further phase of 2 daily dose units of pharmaceutically acceptable placebo in a multiphase combination product having a total number of 28 daily dose units for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception.
3. Use of estradiol valerate or estradiol in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest) as claimed in claim 1, comprising a first phase of 2 daily dose units of 3 mg of estradiol valerate or of less than 3 mg of estradiol, a second phase of 2 groups of daily dose units, where

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the first group comprises 5 daily dose units of a combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 3 mg of dienogest and the second group comprises 17 daily dose units of a combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 4 mg of dienogest, a third phase of 2 daily dose units with 1 mg of estradiol valerate or less than 1 mg of estradiol and a further phase of 2 daily dose units of pharmaceutically acceptable placebo in a multiphase combination product having a total number of 28 daily dose units for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception.

4. Use of estradiol valerate or estradiol in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest) as claimed in claim 1, comprising a first phase of 2 daily dose units of 3 mg of estradiol valerate or of less than 3 mg of estradiol, a second phase of 2 groups of daily dose units, where the first group comprises 5 daily dose units of a combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 1 mg of dienogest and the second group comprises 17 daily dose units of a combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 2 mg of dienogest, a third phase of 2 daily dose units with 1 mg of estradiol valerate or less than 1 mg of estradiol and a further phase of 2 daily dose units of pharmaceutically acceptable placebo in a multiphase combination product having a total number of 28 daily dose units for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception.

5. Use of estradiol valerate or estradiol in

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combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest) as claimed in claim 1, comprising a first phase of 3 daily dose units of 3 mg of estradiol valerate or of less than 3 mg of estradiol,
5 a second phase of 2 groups of daily dose units, where the first group comprises 4 daily dose units of a combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 1 mg of dienogest and the second group comprises 16 daily dose units of a
10 combination of 2 mg of estradiol valerate or less than 2 mg of estradiol and 2 mg of dienogest,
a third phase of 2 daily dose units with 1 mg of estradiol valerate or less than 1 mg of estradiol and a further phase of 3 daily dose units of pharmaceutically
15 acceptable placebo
in a multiphase combination product having a total number of 28 daily dose units for oral therapy for maintaining and/or increasing female libido, where appropriate united with oral contraception.

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6. Use of estradiol valerate or estradiol in combination with 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest), comprising less than or equal to 30 μ g of estradiol valerate or estradiol in combination
25 with less than or equal to 2.00 mg of 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest), in a single-phase combination product
having a total number of 28 daily dose units
or a total number of 21 daily dose units and 7
30 pharmaceutically acceptable placebo-containing or placebo- and hormone-free daily dose units,
or a total number of 22 daily dose units and 6 pharmaceutically acceptable placebo-containing or placebo- and hormone-free daily dose units,
35 or a total number of 23 daily dose units and 5 pharmaceutically acceptable placebo-containing or placebo- and hormone-free daily dose units,

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or a total number of 24 daily dose units and 4
pharmaceutically acceptable placebo-containing or
placebo- and hormone-free daily dose units,
or a total number of 25 daily dose units and 3
5 pharmaceutically acceptable placebo-containing or
placebo- and hormone-free daily dose units,
or a total number of 26 daily dose units and 2
pharmaceutically acceptable placebo-containing or
placebo- and hormone-free daily dose units,
10 or a total number of 27 daily dose units and 1
pharmaceutically acceptable placebo-containing or
placebo- and hormone-free daily dose unit
for oral therapy for maintaining and/or increasing
female libido, where appropriate united with oral
15 contraception.