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(54) Titre : COMBINAISON SEQUENTIELLE OESTROGENE/ANTAGONISTE DE LA PROGESTERONE S'UTILISANT
EN THERAPIE HORMONALE DE SUBSTITUTION
(54) Title: SEQUENTIAL OESTROGEN/PROGESTERONE ANTAGONIST COMBINATION FOR HORMONE
REPLACEMENT THERAPY

(57) **Abrégé/Abstract:**

This invention relates to a pharmaceutical agent that contains in combination individual dosage units of an estrogen and individual dosage units of a competitive progesterone antagonist for separate, sequential administration thereof, which can be used for hormone replacement therapy, as well as packaging that contains this pharmaceutical agent.



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(54) **Title:** SEQUENTIAL ESTROGEN/PROGESTERONE ANTAGONIST
COMBINATION FOR HORMONE REPLACEMENT THERAPY

(57) **Abstract**

This invention relates to a pharmaceutical agent that contains in combination individual dosage units of an estrogen and individual dosage units of a competitive progesterone antagonist for separate, sequential administration thereof, which can be used for hormone replacement therapy, as well as packaging that contains this pharmaceutical agent.

WO 97/33589

PCT/DE97/00580

**Sequential Estrogen/Progesterone Antagonist Combination
for Hormone Replacement Therapy**

This invention relates to a pharmaceutical agent that contains in combination individual dosage units of an estrogen and individual dosage units of a competitive progesterone antagonist for separate, sequential administration thereof, packaging for hormone replacement therapy that contains individual dosage units of an estrogen and individual dosage units of a competitive progesterone antagonist for its separate, sequential administration, and the use of the above-mentioned pharmaceutical agent for hormone replacement therapy.

With the onset of menopause in women, so-called menopausal symptoms occur owing to altered hormone production. Because of reduced estrogen production, the risk of osteoporosis increases at the same time (reduction of bone tissue while retaining the same bone structure, due to increased bone degradation and/or reduced bone growth); likewise in postmenopausal women, a myocardial infarction rate that is significantly increased compared to premenopausal women and an increased incidence of other cardiovascular diseases are observed, which also can be attributed to reduced estrogen production.

Hormone replacement therapy (= HRT) with estrogens or with an estrogen/gestagen combination is currently the standard method for treating the symptoms that are associated with menopause (Ernster, V. L. et al. (1988): Benefits and Risks of Menopausal Estrogen and/or Progestin Hormone Use; Prev. Med. 17:201-223).

Estrogen exerts a protective action on the cardiovascular system, on the bones (reduction of the risk of osteoporosis), and on the central nervous system (avoidance of so-called "hot flashes"). However, the chronic use of estrogens in hormone replacement therapy leads to an increased risk of endometrial carcinoma (Ernster, V. L. et al. (1988): Benefits and Risks of Menopausal Estrogen and/or Progestin Hormone Use; Prev. Med. 17:201-223).

By simultaneously using a gestagen for hormone replacement therapy, the stimulating effect of estrogen on the endometrium is suppressed (Gibbson, W. E., 1986, Biochemical and Histologic Effects of Sequential Estrogen/Progestin Therapy on the Endometrium of Postmenopausal Women; Am. J. Obstet. Gynecol: 154:46-61); in contrast, however, in the case of combined therapy with an estrogen and gestagen, the protective effects of the estrogenic components with respect to the plasma lipids can at least be attenuated (Lobo, R. (1992): The Role of Progestins in Hormone Replacement Therapy; Am. J. Obstet. Gynecol. 166: 1997-2004).

In addition, with an estrogen/gestagen treatment based on a hormone dosage that is lower than with an oral contraceptive agent, undesirable intracyclic menstrual bleeding can occur (Hillard, T. C. et al. (1992): Continuous Combined Conjugated Equine Estrogen-Progestagen Therapy: Effects of Medroxyprogesterone Acetate and Norethindrone Acetate on Bleeding Patterns and Endometrial Histologic Diagnosis; Am. J. Obstet. Gynecol. 167: 1-7).

Finally, recent findings show that many gestagens can increase the risk of breast cancer (Staffa, J. A. et al. (1992): Progestins and Breast Cancer: An Epidemiologic Review; 57: 473-491); King, R. J. B. (1991): A Discussion of the Roles of Estrogen and Progestin in Human Mammary Carcinogenesis; J. Ster. Biochem. Molec. Bio. 39: 8111-8118).

In summary, the picture that forms is that the known estrogen-mono- and estrogen/gestagen combination therapies do not represent any satisfactory options for treating the symptoms that are associated with menopause.

Recently, the use of "true" antiestrogens for the production of pharmaceutical agents for hormone replacement therapy (HRT) has also been proposed (EP-A-0 178 862). "True" antiestrogens refer, according to EP-A-0 178 862, for example, to tamoxifen, nafoxidine, MER-25, as well as those antiestrogens which act in a receptor-mediated manner and which at the same time also have an estrogenic (agonistic) partial action. This estrogenic partial action occurs in the uterus and in bone.

A disadvantage to such a pharmaceutical agent that contains a "true" antiestrogen with a partial estrogenic action is that, owing to the chronically estrogenic stimulation of the endometrium, such as occurs with use of estrogens, an increased risk of the development of an endometrial carcinoma exists (Fornander, T. et al. (1989): Adjuvant Tamoxifen in Early Breast Cancer: Occurrence of New Primary Cancers: Lancet 21: 117-119).

In contrast, positive effects on the bone are produced by the partial estrogenic action of tamoxifen; in women, tamoxifen

seems to partially prevent the degradation of the bone mass (Love, R. R. et al. (1992): Effects of Tamoxifen on Bone Mineral Density in Postmenopausal Women with Breast Cancer; N. Engl. J. Med. 26:852-856).

In addition, studies on tamoxifen have shown that its antiestrogenic component is responsible for growth inhibition when used in the treatment of breast cancer in postmenopausal women (Buckley, M. M. T. et al. (1989); Tamoxifen: A Reappraisal of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use; Drugs 37: 451-490).

In addition, antiestrogens such as raloxifen for inhibiting bone degradation and for treating perimenopausal syndrome have become known (US Patent 5,393,763 or 5,391,557). Antiestrogens of this type show a clearly reduced agonistic (estrogenic) action on the endometrium, but exert a significantly estrogenic action on the bone. Since these substances are also not completely dissociated, however (i.e., they always have a residual estrogenic action on the endometrium), they can also result in a proliferation of the endometrium after long-term treatment.

Accordingly, the necessary chronic use of an antiestrogen with a partial agonistic action in hormone replacement therapy can be considered harmful since stimulation of the endometrium can promote the development of endometrial carcinoma.

WO-EP 94/03408 proposes to avoid this permanent stimulation of the endometrium by simultaneously using a compound with a progesterone-antagonistic action as well as a compound with an antiestrogenic action while at the same time there is a partial

agonistic action for the production of a pharmaceutical agent for hormone replacement therapy. In the case of such a pharmaceutical agent, the component with a progesterone-antagonistic action inhibits the changes that are caused by the partial estrogenic action of the antiestrogen (stimulation of the myometrium and endometrium) only in the uterus, while, however, the other estrogenic effects, which are highly desired in hormone replacement therapy, for example on bone and on the cardiovascular system, remain unchanged.

The administration of an estrogen, optionally together with a gestagen, both at very low dosages, which by themselves do not ensure stable bleeding behavior, combined with a periodic, one-time administration of an antiprogestin (progesterone antagonist) for contraception and for hormone replacement therapy, is described in WO-A 93/17686. The progesterone antagonist ensures a reduction in breakthrough bleeding.

The joint, and preferably simultaneous use of a competitive progesterone antagonist with an estrogen without gestagen is described in WO-A 94/18983. The use of the estrogen according to this publication is done entirely according to the conventional principles of estrogen replacement therapy. The progesterone antagonist is used in an amount that inhibits the endometrial proliferation that is induced by estrogen.

In any case, chronic (e.g., daily) treatment with a progesterone antagonist can lead to side-effects, for example in the liver, because of the daily burden of the organism.

The object of this invention is to provide a pharmaceutical agent which is based on an estrogen and progesterone antagonist for hormone replacement therapy and which has a stronger antiproliferative action on the endometrium than the pharmaceutical agent that is described according to WO-A 93/17686 and WO-A 94/18983.

This object is achieved by this invention, and specifically by a pharmaceutical agent that contains in combination individual dosage units of an estrogen and individual dosage units of a competitive progesterone antagonist in its separate, sequential administration.

This pharmaceutical agent can be used for hormone replacement therapy.

In addition to the pharmaceutical agent, this invention also relates to packaging that contains this pharmaceutical agent.

In the pharmaceutical agent according to the invention, the dosage units that contain the progesterone antagonists are thus used only after a specific length of time during which the exclusively estrogen-containing dosage units were administered. Over the period when the progesterone antagonist is administered, no estrogen is provided. This sequential administration of the progesterone antagonist inhibits proliferation of the endometrium that is otherwise induced by estrogen and in addition reduces the level of estrogen-dependent irregular bleeding. The use of the progesterone antagonist thus results in protection of the endometrium and ultimately induces amenorrhea. In this case, the

protective effect of the estrogen on the bones remains fully intact.

It has been found that such a pharmaceutical agent has, surprisingly enough, a stronger antiproliferative action than the pharmaceutical agents that are produced according to WO-A 93/17686 and WO-A 94/18983.

The stronger antiproliferative action of the pharmaceutical agent according to the invention is due to the stronger antiproliferative action of the progesterone antagonist in the absence of estrogen than when a progesterone antagonist is used simultaneously with an estrogen (WO-A 94/18983). The risk of an "unopposed estrogen effect" is thus reduced.

Advantages of the pharmaceutical agent according to the invention lie in the fact that, with the latter, the positive effects of estrogen on the bones and the lipids are not inhibited and no breakthrough bleeding is induced. This is achieved by avoiding additional stress on the organism, as would be the case with a combined treatment.

It was shown that in the case of ovariectomized Cynomolgus monkeys (as animal models for postmenopausal women), the proliferation of the myometrium or endometrium that is stimulated by estradiol is inhibited by a progesterone antagonist such as RU 486 that is administered over a period of 7 days -- after 28 days when estrogen was administered by itself.

The pharmaceutical agents according to the invention are suitable both for preventive use and for curative use in hormone replacement therapy (HRT), since degradation of bone mass is

prevented by the estrogen and simultaneously the estrogen exerts a protective effect on the cardiovascular system and the undesirable stimulating effect on the endometrium is prevented by the antiproliferative action of the progesterone antagonist.

These pharmaceutical agents are thus especially suitable for long-term use in HRT.

In the pharmaceutical agent according to the invention, the dosage units of the estrogen are intended for administration preferably over a period of 28 to 112 days.

In another embodiment of the pharmaceutical agent according to the invention, the dosage units of the competitive progesterone antagonist are provided for administration over a period of at least 4 days and at most 30 days.

A special embodiment of the pharmaceutical agent according to the invention contains the dosage units of the competitive progesterone antagonist for administration over a period of 7 days.

The pharmaceutical agent according to the invention is preferably designed in such a way that the dosage units of estrogen and the dosage units of the competitive progesterone antagonist are present together in the pharmaceutical agent in such a number that the sum of the number of daily dosage units of the estrogen and the dosage units of the competitive progesterone antagonist is 28 or 28 plus 7 or 28 plus a multiple of 7.

The taking of this embodiment of the pharmaceutical agent according to the invention thus leads to an administration cycle

that lasts exactly a certain number of weeks, but at least four weeks.

As examples, the following compositions can be used:

28 daily units of estrogen + 7 daily units of progesterone antagonist, 28 daily units of estrogen + 14 daily units of progesterone antagonist, 28 daily units of estrogen + 21 daily units of progesterone antagonist, 56 daily units of estrogen + 21 daily units of progesterone antagonist, etc.

Compositions of the pharmaceutical agent according to the invention that are preferred as well are also possible, however, in which the number of the daily dosage units of estrogen and the number of dosage units of the competitive progesterone antagonists are not in each case 7 or a multiple of 7: it is important only that the sum of these daily units can be divided by 7, i.e., the taking of the pharmaceutical agent leads to an exactly 4-week or multiple-week administration cycle.

According to another embodiment, estrogen is present in dosage units that are intended for daily administration.

The progesterone antagonist can also be present in daily oral dosage units.

If the dosage units of the competitive progesterone antagonist are provided for administration over a period of 7 days, these dosage units can advantageously be present in the form of a dosage unit that can be administered once a week.

In such a dosage unit that is to be administered once a week, the progesterone antagonist should preferably be prepared

in a formulation that results in a delayed release of the active ingredient.

A delayed release of the competitive progesterone antagonist can be achieved, for example, by formulating the dosage unit that is to be administered orally as a composite tablet or by providing the dosage unit that is to be administered orally with a timed-disintegration coating, as is readily known to one skilled in the art.

By derivatization, for example by esterification of a free hydroxy group in an effective precursor, the competitive progesterone antagonist that is used for the production of the pharmaceutical agent according to the invention can also have a longer half-life than this precursor. As a result, a longer-lasting action is also achieved. This principle is implemented in, for example, the esters of 11β -[4-N,N-(dimethylamino)phenyl]- 17α -hydroxy- 17β -(3-hydroxypropyl)- 13α -methyl-4,9(10)-gonadien-3-one (onapristone) that are described in EP-A 0 186 834.

The estrogenic aspect of this invention is analogous to conventional estrogen replacement therapy. Consequently, any compound that is effective as estrogen can be used in the known doses and according to the methods that are known for estrogen replacement therapy.

As estrogens, all estrogenically active compounds are suitable for the purposes of this invention.

Estrogens that can be used within the scope of this invention are, for example, ethinylestradiol, 17β -estradiol as well as its esters such as estradiol-3-benzoate, estradiol-17-

valerate, -cypionate, -undecylate, -enanthate and/or other estradiol esters (US-PS 2,611,773, US-PS 2,990,414, US-PS 2,054,271, US-PS 2,225,419 and US-PS 2,156,599) and conjugated estrogens.

Estradiol-, ethinylestradiol- and estrone-3-sulfamates, for example estrone-N,N-dimethylsulfamate, estrone-N,N-diethylsulfamate, ethinylestradiol-3-N,N-dimethylsulfamate, ethinylestradiol-3-N,N-diethylsulfamate, ethinylestradiol-3-N,N-tetramethylenesulfamate, estrone sulfamate, estradiol-3-sulfamate, estradiol-3-N,N-dimethylsulfamate, estradiol-3-N,N-diethylsulfamate, ethinylestradiol-3-sulfamate, which all represent prodrugs for the corresponding 3-hydroxy compounds (W. Elger et al., in J. Steroid Biochem. Molec. Biol., Vol. 55, No. 3/4, 395-403, 1995; DE 44 29 398 A1 and DE 44 29 397 A1), can also be used in the pharmaceutical agent according to the invention.

Finally, the orally bioavailable derivatives of 17β - and 17α -estradiol with a modified D-ring of the steroid skeleton are also suitable.

The use of a natural estrogen (also conjugated estrogens) or a prodrug of a natural estrogen is preferred according to the invention.

The progesterone antagonist is preferably selected for this invention from the group of compounds

11β -[4-(dimethylamino)phenyl]- 17β -hydroxy- 17α -(1-propinyl)estra-4,9-dien-3-one (RU 38 486)

11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(1-propinyl)-
18a-homoestra-4,9-dien-3-one

11 β -[4-(dimethylamino)phenyl]-17a β -hydroxy-17a α -(1-
propinyl)-17a-homoestra-4,9,16-trien-3-one

17 α -ethinyl-17 β -hydroxy-11 β -(4-methoxyphenyl)estra-4,9-dien-
3-one

11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1-propinyl)estra-4,9-
dien-3-one

the 19,11 β -bridged steroids from EP-A 0283 428,

the 10 β -H steroids from EP-A 0 404 283, especially

(Z)-11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-
hydroxy-1-propenyl)estr-4-en-3-one

11 β -[4-(dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-
hydroxypropyl)-13 α -estra-4,9-dien-3-one (onapristone)

(Z)-11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(3-hydroxy-1-
propenyl)estra-4,9-dien-3-one

(Z)-6'-(4-cyanophenyl)-9,11 α -dihydro-17 β -hydroxy-17 α -(3-
hydroxy-1-propenyl)-4'H-naphth[3',2',1':10,9,11]estra-4,9(11)-
dien-3-one

(Z)-9,11 α -dihydro-17 β -hydroxy-17 α -(3-hydroxy-1-propenyl)-6'-
(3-pyridinyl)-4'H-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-
one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]-6 β -
methylspiro[estra-4,9-diene-17 β ,2'(3'H)-furan]-3-one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]-7 β -
methylspiro[estra-4,9-diene-17 β ,2'(3'H)-furan]-3-one

11 β -(4-acetylphenyl)-19,24-dinor-17,23-epoxy-17 α -chola-4,9,20-trien-3-one.

Especially preferred for the purposes of this invention are the progesterone antagonists

11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(1-propenyl)estra-4,9-dien-3-one (RU 38 486)

(Z)-11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-hydroxy-1-propenyl)estr-4-en-3-one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]-6 β -methylspiro[estra-4,9-diene-17 β -2' (3'H)-furan]-3-one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]-7 β -methylspiro[estra-4,9-diene-17 β ,2' (3'H)-furan]-3-one

11 β -(4-acetylphenyl)-19,24-dinor-17,23-epoxy-17 α -chola-4,9,20-trien-3-one.

For the purposes of this invention, the formulation of the estrogen and progesterone antagonist is done in a completely conventional manner, as is already known for the formulation of these compounds for their individual use in hormone replacement therapy for estrogen, for example Cyclo-Progynova[™], or in tumor therapy or for abortion for progesterone antagonists, for example mifepristones.

In particular, reference is also made to the information that is contained in WO-A 93/17686 and WO-A 94/18983.

In addition to oral administration of the estrogen and the progesterone antagonist, it is equally possible to administer one or both of the components transdermally, for example with a skin

patch, which is best known for the administration of estrogen (Climara Patch).TM

In addition, administration can be done using an intrauterine release system, but this variant is not preferred within the scope of this invention.

The administration of one or both components as a depot formulation is also possible.

Finally, all above-mentioned types of administration can be combined. For example, the estrogen can be administered transdermally with a skin patch, and the progesterone antagonist can be administered daily orally or one or more times as a depot formulation.

The estrogen is contained per daily dosage unit according to the invention in an amount of 1 to 2 mg of estradiol or a bioequivalent amount of another estrogen.

As bioequivalent amounts of other estrogens for the purposes of this invention, the following amounts can be considered:

ethinylestradiol 5-35 μ g

conjugated estrogens 0.625 to 1.25 mg.

In the case of transdermal administration of the estrogen, the transdermal administration system should release daily approximately 50 μ g of estradiol or a bioequivalent amount of another estrogen.

The administration of the estrogen using a vaginal cream or vaginal ring is also possible. The daily amounts are about 1.25 mg or 0.2 mg in the case of estradiol. In this case, these are only approximate values.

In the pharmaceutical agent according to the invention, the competitive progesterone antagonist is contained in each dosage unit preferably in an amount such that, when used over the intended length of time, it is sufficient for amenorrhea to occur.

In an especially preferred embodiment of the pharmaceutical agent according to the invention, the competitive progesterone antagonist is contained in each daily dosage unit in an amount that is equivalent to 0.5 mg to 10 mg, preferably 1 mg to 5 mg of RU 486.

The packaging that contains the pharmaceutical agent according to the invention is prepared in such a way that, in addition to the two components estrogen, or an antiestrogen with partial agonistic action, and progesterone antagonist in the respectively intended form of administration (orally in the form of pills, coated tablets, etc. in a blister pack, as may be appropriate for estrogen and/or progesterone antagonists, or the estrogen as a skin patch and the progesterone antagonist in the form of pills, coated tablets, etc. in a blister or in a capsule as a depot that is to be administered once), said packaging also contains instructions for the use of the pharmaceutical agent (package insert). Particularly, said packaging contains instructions for administration of the dosage units of estrogen, or antiestrogen with a partial agonistic action, in the absence of dosage units of the competitive progesterone antagonist.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Pharmaceutical agent comprising in combination individual dosage units of an estrogen and individual dosage units of a competitive progesterone antagonist for separate, sequential administration thereof, in which administration of the competitive progesterone antagonist is in the absence of the estrogen.

2. Pharmaceutical agent according to claim 1, in which the dosage units of the estrogen are intended for administration over a period of 28 to 90 days.

3. Pharmaceutical agent according to claim 1, in which the dosage units of the estrogen are intended for administration over a period of 28 to 30 days.

4. Pharmaceutical agent according to claim 1, in which the dosage units of the estrogen are prepared for oral administration.

5. Pharmaceutical agent according to claim 1, in which the dosage units of the estrogen are prepared for transdermal administration.

6. Pharmaceutical agent according to claim 1, in which the dosage units of the competitive progesterone antagonist are intended for administration over a period of at least 4 days to at most 30 days.

7. Pharmaceutical agent according to claim 6, in which the dosage units of the competitive progesterone antagonist are intended for administration over a period of 7 days.

8. Pharmaceutical agent according to claim 7, in which the dosage units of the estrogen are intended for administration over a period of 28 to 30 days.

9. Pharmaceutical agent according to claim 7, in which the dosage units of the estrogen are intended for administration over a period of 60 days.

10. Pharmaceutical agent according to claim 5, in which the dosage units of the competitive progesterone antagonist are intended for administration over a period of 20 days.

11. Pharmaceutical agent according to any one of claims 1 to 10, characterized in that the dosage units of the estrogen and the dosage units of the competitive progesterone antagonist together are present in the pharmaceutical agent in such a number that the sum of the number of daily dosage units of the estrogen and the dosage units of the competitive progesterone antagonist is 28 or 28 plus 7 or 28 plus a multiple of 7.

12. Pharmaceutical agent according to claim 1, wherein the dosage units of the progesterone antagonist are prepared for oral administration.

13. Pharmaceutical agent according to claim 1, wherein the dosage units of the progesterone antagonist are present as a depot formulation for administration one or more times.

14. Pharmaceutical agent according to claim 1, wherein each individual dosage unit of the estrogen is a daily dosage unit.

15. Pharmaceutical agent according to claim 1, in which each individual dosage unit of the competitive progesterone antagonist is a daily dosage unit.

16. Pharmaceutical agent according to claim 7, wherein the dosage units are present in the form of a dosage unit for administration once a week.

17. Pharmaceutical agent according to claim 1, wherein the estrogen is selected from the group of compounds consisting of ethinylestradiol, 17 β -estradiol, estradiol-3-benzoate, estradiol-17-valerate, -cypionate, -undecylate, -enantate, conjugated estrogens, estrone-N,N-dimethylsulfamate, estrone-N,N-diethylsulfamate, ethinylestradiol-3-N,N-dimethylsulfamate, ethinylestradiol-3-N,N-diethylsulfamate, ethinylestradiol-3-N,N-tetramethylenesulfamate, estrone sulfamate, estradiol-3-sulfamate, estradiol-3-N,N-dimethylsulfamate, estradiol-3-N,N-diethylsulfamate, ethinylestradiol-3-sulfamate, and combinations thereof.

18. Pharmaceutical agent according to claim 17, wherein the estrogen is a natural estrogen.

19. Pharmaceutical agent according to claim 1, wherein the competitive progesterone antagonist is selected from the group of compounds consisting of

11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(1-propinyl)estra-4,9-dien-3-one (RU 486)

11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(1-propinyl)-18a-homoestra-4,9-dien-3-one

11 β -[4-(dimethylamino)phenyl]-17 $\alpha\beta$ -hydroxy-17 $\alpha\alpha$ -(1-propinyl)-17a-homoestra-4,9,16-trien-3-one

17 α -ethinyl-17 β -hydroxy-11 β -(4-methoxyphenyl)estra-4,9-dien-3-one

11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1-propinyl)estra-4,9-dien-3-one

11 β -[4-(dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -estra-4,9-dien-3-one (onapristone)

(Z)-11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-hydroxy-1-propenyl)estr-4-en-3-one

(Z)-11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(3-hydroxy-1-propenyl)estra-4,9-dien-3-one

(Z)-6'-(4-cyanophenyl)-9,11 α -dihydro-17 β -hydroxy-17 α -(3-hydroxy-1-propenyl)-4'H-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-one

(Z)-9,11 α -dihydro-17 β -hydroxy-17 α -(3-hydroxy-1-propenyl)-6'-(3-pyridinyl)-4'H-naphth[3',2',1':10,9,11]estra-4,9(11)-dien-3-one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]-6 β -methylspiro[estra-4,9-diene-17 β ,2'(3'H)-furan]-3-one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]7 β -methylspiro[estra-4,9-diene-17 β ,2'(3'H)-furan]-3-one

11 β -(4-acetylphenyl)-19,24-dinor-17,23-epoxy-17 α -chola-4,9,20-trien-3-one, and combinations thereof.

20. Pharmaceutical agent according to claim 19, wherein the competitive progesterone antagonist is consisting of

11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(1-propinyl)estra-4,9-dien-3-one (RU 38 486)

(Z)-11 β -[4-(dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-hydroxy-1-propenyl)estr-4-en-3-one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]-6 β -methylspiro[estra-4,9-diene-17 β ,2'(3'H)-furan]-3-one

4',5'-dihydro-11 β -[4-(dimethylamino)phenyl]-7 β -methylspiro[extra-4,9-diene-17 β ,2'(3'H)-furan]-3-one

11 β -(4-acetylphenyl)-19,24-dinor-17,23-epoxy-17 α -chola-4,9,20-trien-3-one, and combinations thereof.

21. Pharmaceutical agent according to claim 1, wherein the estrogen is contained in an amount of 1 to 2 mg of estradiol or a bioequivalent amount of another estrogen in a daily dosage unit.

22. Pharmaceutical agent according to claim 1, wherein the competitive progesterone antagonist is contained in an amount that triggers amenorrhea.

23. Pharmaceutical agent according to claim 22, wherein the competitive progesterone antagonist is contained in an amount that is equivalent to 0.5 mg to 10 mg of RU 486 in a daily dosage unit.

24. Pharmaceutical agent according to any one of claims 1 to 23 for use for hormone replacement therapy.

25. Packaging for hormone replacement therapy that contains individual dosage units of an estrogen, or antiestrogen with a partial agonistic action, and individual dosage units of a competitive progesterone antagonist for separate, sequential administration, thereof, and instructions for administration of the dosage units of estrogen, or antiestrogen with a partial agonistic action, and the dosage units of the competitive progesterone antagonist, in which the administration of the competitive progesterone antagonist is in the absence of the estrogen, or antiestrogen with a partial agonistic action.