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Preparation for substitution therapy, containing at least one progestogen and at least one estrogen

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(54) Title: PREPARATION FOR SUBSTITUTION THERAPY, CONTAINING AT LEAST ONE PROGESTOGEN AND AT LEAST ONE EXTROGEN

(57) Abstract

The invention relates to a preparation for substitution therapy and oral contraception comprising at least one progestogen and at least one estrogen in which the estrogen dose varies with a periodicity such that blood loss is substantially avoided, wherein the periodicity is preferably less than 10 days, more preferably less than 7 days, such as preparations containing the progestogen and/or estrogen in an oral, transdermal, parenteral and/or implantable application form.

PREPARATION FOR SUBSTITUTION THERAPY, CONTAINING AT LEAST ONE PROGESTOGEN AND AT LEAST ONE ESTROGEN.

The present invention relates to a preparation for substitution therapy and for oral contraception. More particularly the present invention on the one hand relates to relieving the effects which occur because the ovaries decrease or stop production of female hormones, for instance during the menopause. The substitution therapy is mainly intended to induce amenorrhoea with negligible blood loss.

During and after the menopause these effects comprise hot flushes and nocturnal sweating, atrophy of the vagina which can result in sexual difficulties, bone decalcification, increase in heart and blood vessel disorders and psychic symptoms with a causal connection that is usually difficult to demonstrate.

Up to the present different types of substitution therapy have been applied comprising a hormone treatment with one or more oestrogens and one or more progestogens.

According to a first therapy, low doses of oestrogens and progestogens are administered, but such a treatment is ineffective in respect of the decalcification and heart and blood vessel disorders.

In another therapy the natural cycle of oestrogen and progestogen is followed as closely as possible. This treatment inevitably results in menstruation and has the advantage of a reduced risk of cancer of the uterus.

According to yet another therapy only oestrogens are administered in a dose which lies below the threshold for menstrual bleeding. This treatment has the drawback however of an increased risk of cancer of the uterus.

According to a most recently known therapy oestrogens and progestogens are administered continuously such that the endometrium does not proliferate. This therapy has the drawback however of an unacceptably high incidence of slight, irregular blood loss.

CONFIRMATION COPY

The present invention relates to preparations designed for substitution therapy or oral contraception with substantially continuous application.

EP-A-559 240 discloses preparations for substitution therapy and oral contraception in which the estrogen dose is constant and the progestogen dose is periodically alternated. However, the improvement in inhibiting endometrium bleeding is minor. Above that, since the use of higher progestogen doses provided better results than lower doses it appears illogical to use periodically varying estrogen doses.

The present invention is based on the finding that surprising when using periodically varying estrogen doses the occurrence of blood loss and intermediate bleeding is substantially avoided. The estrogen dose is herein oscillated such that estrogen-dominant and progestogen-dominant periods occur alternatingly with a sufficiently short periodicity. This short periodicity in the estrogen dose is necessary to avoid blood loss.

Purely by administering a dose of progestogen substantially constant in time and an estrogen varying in time between at least two dose levels, it was possible to induce the desired amenorrhoea while no blood loss occurred over a longer period.

According to a first aspect, the invention provides a method of substitution therapy and/or oral contraception comprising the step of administering to a subject in need of hormone substitution therapy or oral contraception at least one progestogen and at least one estrogen wherein the progestogen dose is constant, and the estrogen dose varies to oscillate between an estrogen dominant period and a progestogen dominant period with a periodicity of less than 10 days.

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According to a second aspect, the invention provides a dosage arrangement for substitution therapy and/or oral contraception when used according to the first aspect comprising at least one progestogen, at least one estrogen and dosage means in association therewith to ensure that the progestogen dose is constant, and the estrogen dose varies to oscillate between an estrogen dominant period and a progestogen dominant period with a periodicity of less than 10 days.

In a third aspect, the invention consists in the use of at least one progestogen and at least one estrogen for the manufacture of a medicament for substitution therapy and/or oral contraception, wherein the progestogen dose is constant and the estrogen dose varies to oscillate between an estrogen dominant and a progestogen dominant period with a periodicity of less than 10 days.

Unless the context clearly requires otherwise, throughout the description and the Claims, the words 'comprise', 'comprising', and the like are to be construed in an inclusive as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

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It is noted that the preparation is formulated such that a substantially constant blood concentration is obtained for progestogen, while the estrogen concentration in the blood varies between two blood concentrations. The periodicity must be sufficiently short and is generally less than 10 days. The periodicity is usually less than 7 days. The periodicity generally lies between 2-9 days, preferably between 2-6 days. It will, however, be apparent that the periodicity is dependent on the estrogens and progestogens used and the applied doses. Both the periodicity and concentrations of estrogen and progestogen are easy to determine by routine experimentation.

According to an embodiment of the invention the preparation contains a constant progestogen dose, while the estrogen dose oscillates between two levels. This preparation is recommended because there is a greater certainty of avoiding blood loss over a longer period.

According to another embodiment the preparation contains oscillating doses of progestogen and estrogen, in varying ratios however such that blood less is avoided and amenorrhoea is induced.

Use can be made in general of all known progestogens, such as

progesterone	300-900 mg/day
norethisterone acetate	2-5 mg/day
medroxyprogesterone acetate	1-5 mg/day
d-norgestrel	30-150 µgr/day
desogestrel	30-150 µgr/day
norgestimate	30-150 µgr/day
cyproterone acetate	0.2-2 mg/day

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gestodene	10-150 µg/day
3-ketodesogestrel	10-150 µg/day
drospirenon	0.2-3.0 mg/day

or combinations thereof. It is noted that the preparation can contain one or more progestogens and estrogens.

It will be apparent that the quantity of progestogen and estrogen depends on the person (constitution and age),

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the progestogen(s) and estrogen(s), anti-progestogen and anti-estrogen for use and the form of administering same.

The progestogen and estrogen can each be present in an oral, transdermal, parenteral or implantable application form for substitution therapy. The preparation can for instance comprise an application form which contains the progestogen and estrogen, and a second like application form which contains the progestogen and an increased dose of estrogen. The progestogen and estrogen can of course be present in like but separate forms of application or in mutually differing forms of application. The progestogen can for instance be an implantable application form while the oestrogen is administered orally, transdermally or parenterally in a dose which takes account of the required time period according to the invention.

The oral application form to be used comprises tablets, capsules, syrup, solutions. The transdermal forms of application comprise gels, plasters. Strips can for instance be used wherein tablets with progestogen and oestrogen in the desired ratio and periodicity are arranged in time sequence. The parenteral application form comprises injection fluid and the like. The implantable application form comprises for example a known implantable sustained release preparation.

The preparations for oral contraceptive comprise estrogens and progestogens in common form.

Preparations according to the invention were administered over a period of 3-12 months to 40 women in the menopause. By making use of the combination preparations according to the invention a constant amenorrhoea could be obtained in the case of more than 90% of the women, wherein the clinical tolerance was perceived as optimal, wherein the woman did not discern any subjective difference between a fixed or changing oestrogen dose with a periodicity of about one week.

Using the preparations according to the invention as oral contraceptive intermediate bleeding will be substantially reduced.

Example 1

A preparation according to the invention comprised tablets of the type A which contained 10 gamma aethinyl-estradiol, 1 mg estradiol valerianate and 0.5 mg norethisterone, and tablets of the type B which contained 15 gamma instead of 10 gamma aethinyl-estradiol. By alternatingly administering the tablets A and B over a time period of 7 days an amenorrhoea could be induced without blood loss for a very long period of time.

Example 2

A preparation according to the invention comprised tablets of the type A which contained 1 mg norethisterone or 0.5 mg cyproterone acetate and 2 mg estradiol valerianate. The preparation moreover contained tablets of the type B having 3 mg instead of 2 mg estradiol valerianate. By using the preparation with alternate administering (4-5 days) of the tablets A and B or B and A an amenorrhoea could be induced without blood loss for a longer period of time.

Example 3

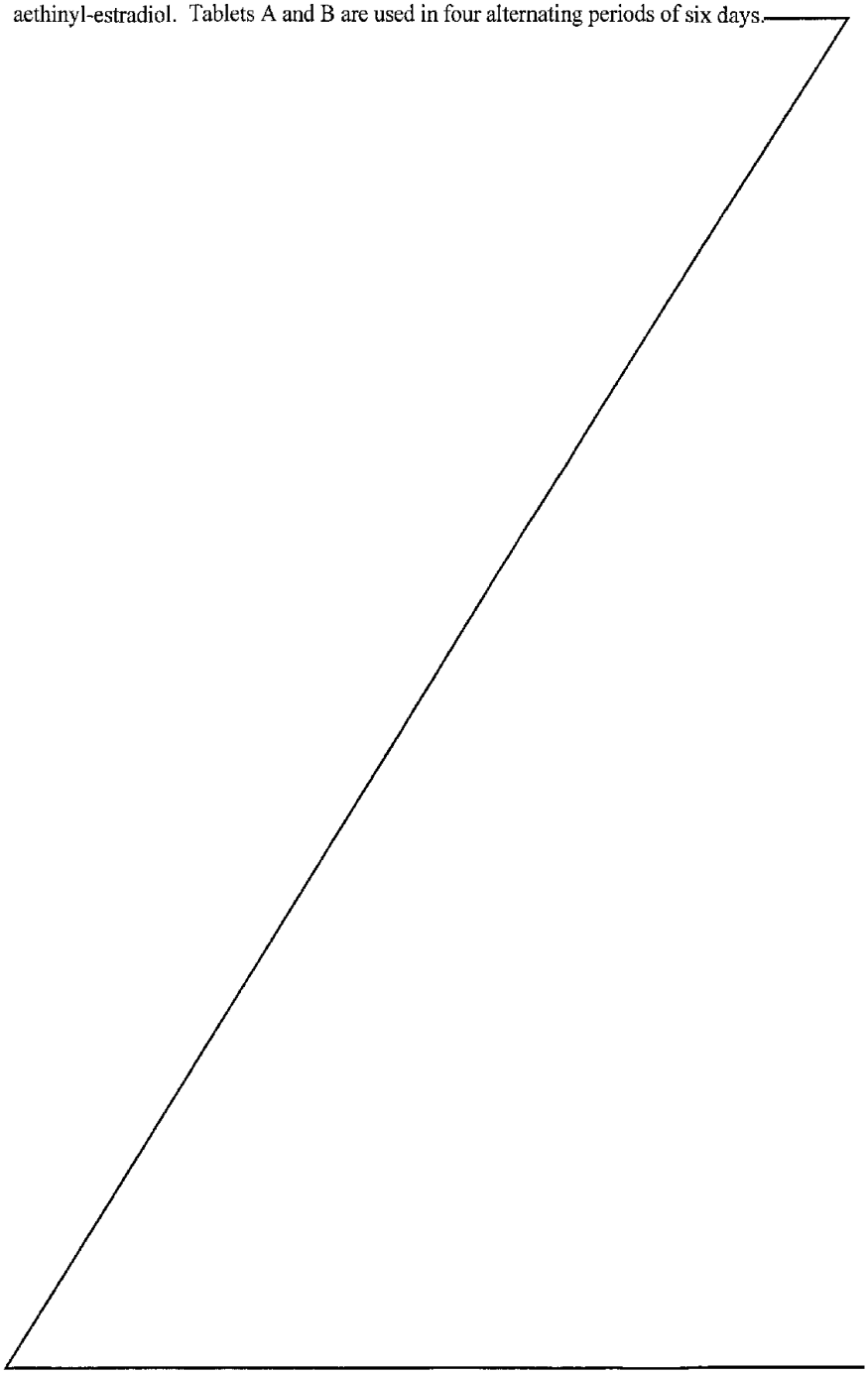
A preparation according to the invention comprised tablets of the type A which contained 15 gamma aethinyl-estradiol and 1 mg oestradiol valerianate and 1 mg norethisterone. The preparation moreover contained tablets of the type B having 1.5 mg instead of 1 mg norethisterone. By alternatingly administering the tablets A and B with a periodicity of 4-7 days an amenorrhoea could be induced without blood loss for a very long period of time.

Example 4

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 20 µg aethinyl-estradiol and 75 µg

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gestoden. The preparation contained tablets of type B comprising 30 µg instead of 20 µg aethinyl-estradiol. Tablets A and B are used in four alternating periods of six days.



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Example 5

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 15 µg aethinyl-estradiol and 75 µg instead of 15 µg aethinyl-estradiol. Tablets A and B are used in six alternating periods of four days.

In example 4 and 5 only aethinyl-estradiol is used in order to use a estrogen dose which is as low as possible. However, higher estrogen doses may be used. Instead of using a constant progestogen dose fluctuating doses may be use fluctuating simultaneously and/or progressively in view of the varying estrogen dose.

Example 6

A preparation for oral contraceptive according to the invention comprises tablets of type A comprising 20µg aethinyl-estradiol and 75 µg gestoden, and tablets of type B comprises 30 µg aethinyl-estradiol and 75 µg gestoden and 50 µg onapristone. The tablets A and B are used in four alternating periods of each six days. After four periods the whole cycle is repeated without allowing a free period.

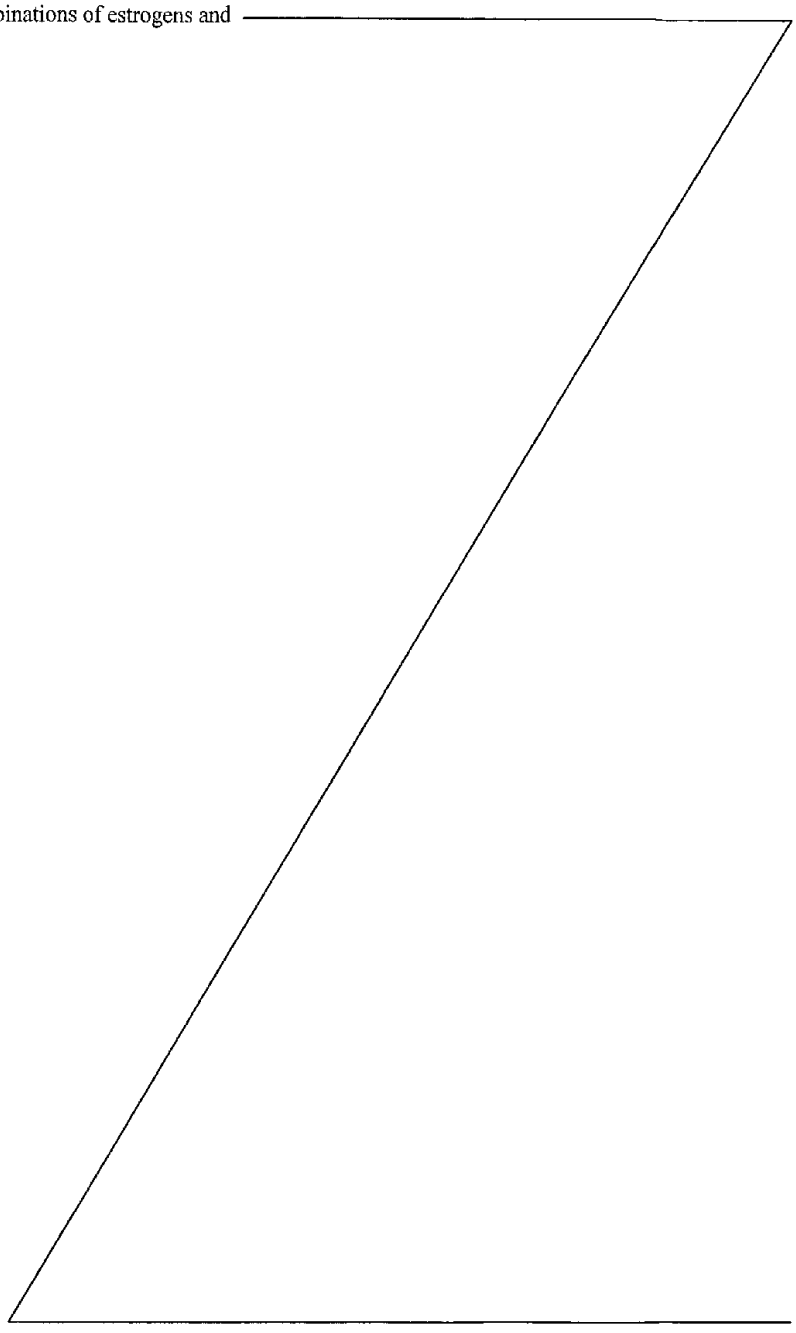
Example 7

A preparation according to the invention for hormone substitution treatment comprises tablets of type A comprising 2 µg estradiol valerianate and 50 µg gestoden. The tablets of type B comprised 3 µg estradiol valerianate and 25-100 µg onapristone. By alternatingly administering the tablets A and B over a time period of seven days amenorrhoea could be induced without blood loss for a very long period of time.

It is obvious for a skilled person in the examples that administration of antiprogestogen or anti-estrogen can be alternated (alone or simultaneously) with estrogens and/or progestogens.

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For instance, the antiprogestogen is added in a constant dose to the abovementioned combinations of estrogens and



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progestagens in products for hormone replacement therapy and for contraception.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of substitution therapy and/or oral contraception comprising the step of administering to a subject in need of hormone substitution therapy or oral contraception at least one progestogen and at least one estrogen wherein the progestogen dose is constant, and the estrogen dose varies to oscillate between an estrogen dominant period and a progestogen dominant period with a periodicity of less than 10 days.

2. A method according to Claim 1 wherein the dosage of estrogen is selected to avoid blood loss.

3. A method according to Claim 1 or Claim 2 wherein a period of oscillation of the estrogen dose is less than 7 days.

4. A method according to Claim 1 or Claim 2 wherein a period of oscillation of the estrogen dose in between 2 and 9 days.

5. A method according to any one of Claims 1 to 4 wherein a period of oscillation of the estrogen dose is between 2 and 6 days.

6. A method according to any one of Claims 1 to 5 wherein the doses of progestogen and estrogen are selected to avoid blood loss.

7. A dosage arrangement for substitution therapy and/or oral contraception when used in a method according to claim 1 comprising at least one progestogen, at least one estrogen and dosage means in association therewith to ensure that the progestogen dose is constant and the estrogen dose varies to oscillate between an estrogen

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dominant period and a progestogen dominant period with a periodicity of less than 10 days.

8. A dosage arrangement according to Claim 7 wherein the dosage of estrogen is selected to avoid blood loss.

9. A dosage arrangement according to Claim 7 or Claim 8 wherein a period of oscillation of the estrogen dose is less than 7 days.

10. A dosage arrangement according to Claim 7 or Claim 8 wherein a period of oscillation of the estrogen dose is between 2 and 9 days.

11. A dosage arrangement according to any one of Claims 7 to 10 wherein a period of oscillation of the estrogen dose is between 2 and 6 days.

12. A dosage arrangement according to any one of Claims 7 to 11 wherein the doses of progestogen and estrogen are selected to avoid blood loss.

13. A dosage arrangement according to any one of Claims 7 to 12 wherein the progestogen is selected from one or more members of the group consisting of

progesterone	300-900 mg/day
norethisterone acetate	2-5 mg/day
medroxyprogesterone acetate	1-5 mg/day
d-norgestrel	30-150 µgr/day
desogestrel	30-150 µgr/day
norgestimate	30-150 µgr/day
cyproterone acetate	0.2-2 mg/day
gestodene	10-150 µg/day

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3-Ketodesogestrel	10-150 µg/day and
drospirenon	0.2-3.0 mg/day

14. A dosage arrangement according to any one of Claims 7 to 13 wherein the estrogen is selected from one or more members of the group consisting of

aethinylestradiol	5-15 gamma/day
oestradiol valerianate	1-4 mg/day
oestradiol	1-2 mg/day
conjugated oestragen	0.3-1.25 mg/day and
oestriol	1-4 mg/day

15. A dosage arrangement according to any one of Claims 7 to 14 wherein the progestogen or estrogen further contains anti-progestogen.

16. A dosage arrangement according to any one of Claims 7 to 15 wherein the progestogen or estrogen further contains anti-estrogen.

17. A dosage arrangement according to any one of Claims 7 to 16 wherein the estrogen is formulated for oral administration.

18. A dosage arrangement according to any one of Claims 7 to 16 wherein the estrogen is formulated for transdermal administration.

19. A dosage arrangement according to any one of Claims 7 to 16 wherein the estrogen is formulated for parenteral administration.

20. A dosage arrangement according to any one of Claims 7 to 16 wherein the estrogen is formulated for an implant.

21. A dosage arrangement according to any one of Claims 7 to 20 wherein the progestogen is formulated for oral administration.

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22. A dosage arrangement according to any one of Claims 7 to 20 wherein the progestogen is formulated for transdermal administration.

23. A dosage arrangement according to any one of Claims 7 to 20 wherein the progestogen is formulated for parenteral administration.

24. A dosage arrangement according to any one of Claims 7 to 20 wherein the progestogen is formulated for an implant.

25. A dosage arrangement according to any one of Claims 7 to 20 wherein the dosage means has discrete dosage forms with progestogen and estrogen in the desired ratio and periodicity arranged in time sequence.

26. A dosage arrangement according to Claims 25 wherein the discrete dosage form is a tablet or capsule.

27. The use of at least one progestogen and at least one estrogen for the manufacture of a medicament for substitution therapy and/or oral contraception, wherein the progestogen dose is constant and the estrogen dose varies to oscillate between an estrogen dominant period and a progestogen dominant period with a periodicity of less than 10 days.

28. The use of Claim 27 wherein the dosage of estrogen is selected to avoid blood loss.

29. The use of claim 27 or 28 wherein a period of oscillation of the estrogen dose is less than 7 days.

30. The use of Claim 27 or 28 wherein a period of oscillation of the estrogen dose is between 2 and 9 days.

31. The use of any one of Claims 27 to 30 wherein a period of oscillation of the estrogen dose is between 2 and 6 days.

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32. The use of any one of Claims 27 to 31 wherein the doses of progestogen and estrogen are selected to avoid blood loss.

33. A dosage arrangement for substitution therapy and/or oral contraception when used in a method according to any one of claims 1-6 substantially as herein described with reference to any one of the examples, but not including comparative examples.

34. A method of hormone substitution therapy and/or oral contraception substantially as herein described with reference to any one of the examples, but not including comparative examples.

35. A dosage arrangement for substitution therapy and/or oral contraception when used in a method according to claim 34 comprising a progestogen, an estrogen and dosage means in association therewith to ensure the progestogen dose is constant and the estrogen dose oscillates between an estrogen dominant period and a progestogen dominant period with a periodicity of less than 10 days substantially as herein described with reference to any one of the examples.

36. The use of at least one progestogen and at least one estrogen for the manufacture of a medicament for substitution therapy and/or oral contraception substantially as herein described with reference to any one of the examples.

DATED this 15th Day of June 1999

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