Aspect 25. The E4 composition for use according to any one of aspects 22 to 24, for use in reducing the risk of elevated C-reactive protein (CRP) blood serum concentration levels associated with the continuous use of a combined oral contraceptive comprising DRSP.

Aspect 26. E4 for use in lowering the steady state bioavailability of DRSP in a COC with at least 15% as compared to COC's comprising equivalent amounts of DRSP and EE, preferably with at least 20%, more preferably with at least 25% such as about 30% or more.

Aspect 27. E4 for use in lowering the peak blood plasma concentration of DRSP in subjects continuously using COC's comprising DRSP.

Aspect 28. A method for reducing the risk of adverse effects of DRSP in a subject under a continuous regimen of a COC comprising DRSP, comprising the step of providing a COC comprising DRSP as the progestogenic component and E4 as the estrogenic component.

Aspect 29. A COC comprising E4 and DRSP for use in reducing side effects of DRSP associated with the continuous use of a combined oral contraceptive comprising DRSP. The "continuous use" implies that the dosage-regime is applied for multiple periodic cycles. Typically one periodic cycle comprises the application of 21 to 28 daily dosage units of COC comprising the active ingredients. Said use can in some cases be interrupted between the different periodic cycles for 4 to 7 days, optionally by providing placebo dosage units not comprising the active ingredients of the COC, or simply by not taking any pills for those 4 to 7 days. Typically a 21-28 dosage unit regimen of active COC ingredients is applied, interrupted by a 4 to 7 day use of placebo dosage units for compliance reasons.

Aspect 30. Use of E4 for the manufacture of a medicament for the prevention or treatment of adverse effect attributable to the use of DRSP in a COC.

Aspect 31. Use of E4 for the manufacture of a composition (i.e. medicament or contraceptive) for the prevention or treatment of QT interval prolongation in subjects using a DRSP comprising COC.

Aspect 32. Use of E4 for the manufacture of a composition (i.e. medicament or contraceptive) for the prevention or treatment of free testosterone blood serum level reduction in subjects using a DRSP comprising COC.

Aspect 33. Use of E4 for the manufacture of a composition (i.e. medicament or contraceptive) for the prevention or treatment of a C-reactive protein level increase in subjects using a DRSP comprising COC.

In one aspect, there is provided use of a composition comprising drospirenone (DRSP) as progestogenic component in an amount of between 1 mg to 5 mg and estetrol as estrogenic component in an amount of between 10 mg and 20 mg in the manufacture of a medicament formulated as a combined oral contraceptive (COC) for reducing the risk of one or more DRSP-related adverse effects in a subject associated with the use of a COC comprising DRSP and an estrogenic component, wherein the subject has experienced one or more DRSP-related adverse effects, wherein the one or more adverse effects are selected from the group consisting of:

- a QT interval prolongation by at least 5 milliseconds,
- a reduction of the free testosterone blood plasma concentration, and
- an increase of the C-reactive protein blood plasma concentration;

and wherein the following pharmacokinetic profile for drospirenone in blood plasma is provided when administered daily:

(i) a geometric mean AUC0-24 of drospirenone between about 150 and about 1000 ng.h/ml; and/or

(ii) a geometric mean Cmax of drospirenone between about 10 ng/ml and 100 ng/ml.

In any one of the above listed aspects or embodiments herein, the preferred amount of estetrol in said COC is equivalent to an amount of 14 to 16 mg of estetrol and can be present in the form of estetrol

monohydrate in a range of between 14 and 16 mg, preferably in an amount of 15 mg estetrol monohydrate or its equivalent 14,2 mg estetrol.

In any one of the above listed aspects or embodiments, the preferred amount of drospirenone is said COC is equivalent to about 2 to 4 mg or from about 2,5 to 3,5 mg drospirenone.

The above and further aspects and preferred embodiments of the disclosure are described in the following sections and in the appended claims. The subject matter of the appended claims is hereby specifically incorporated in this specification.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Subject stratification. 98 subjects were enrolled in a treatment with E4/DRSP 15/3 mg (n=38), EE/LNG 0.03/0.15 mg (n= 29), EE/DRSP 0.02/3 mg (n=31). AE: adverse effects.

Figure 2. Changes in QTcF interval at treatment cycle 3, day 24. Treatment group: E4/DRSP 15/3 mg, reference group: EE/DRSP 0.02/3 mg.

Figure 3. Changes in QTcF interval at treatment cycle 3, day 27. Treatment group: E4/DRSP 15/3 mg, reference group: EE/DRSP 0.02/3 mg.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the singular forms “a”, “an”, and “the” include both singular and plural referents unless the context clearly dictates otherwise.

The terms “comprising”, “comprises” and “comprised of” as used herein are synonymous with “including”, “includes” or “containing”, “contains”, and are inclusive or open-ended and do not exclude additional, non-recited members, elements or method steps. The terms also encompass “consisting of” and “consisting essentially of”, which enjoy well-established meanings in patent terminology.

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within the respective ranges, as well as the recited endpoints. This applies to numerical ranges irrespective of whether they are introduced by the expression “from… to…” or the expression “between… and…” or another expression.

The terms “about” or “approximately” as used herein when referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, are meant to encompass variations of and from the specified value, such as variations of +/-10% or less, preferably +/-5% or less, more preferably +/-1% or less, and still more preferably +/-0.1% or less of and from the specified value, insofar such variations are appropriate to perform in the disclosed invention. It is to be understood

CLAIMS

1. Use of a composition comprising drospirenone (DRSP) as progestogenic component in an amount of between 1 mg to 5 mg and estetrol as estrogenic component in an amount of between 10 mg and 20 mg in the manufacture of a medicament formulated as a combined oral contraceptive (COC) for reducing the risk of one or more DRSP-related adverse effects in a subject associated with the use of a COC comprising DRSP and an estrogenic component, wherein the subject has experienced one or more DRSP-related adverse effects, wherein the one or more adverse effects are selected from the group consisting of:

- a QT interval prolongation by at least 5 milliseconds,
- a reduction of the free testosterone blood plasma concentration, and
- an increase of the C-reactive protein blood plasma concentration;

and wherein the following pharmacokinetic profile for drospirenone in blood plasma is provided when administered daily:

(i) a geometric mean AUC0-24 of drospirenone between about 150 and about 1000 ng.h/ml; and/or

(ii) a geometric mean Cmax of drospirenone between about 10 ng/ml and 100 ng/ml.

2. The use according to claim 1, wherein said subject is using said COC continuously in cycles of 21 to 28 daily active dosage units of said composition.

3. The use according to claim 1 or 2, wherein one or more adverse effects of DRSP are reduced compared to a subject under use of a composition having an equivalent effective amount of DRSP and another estrogen.

4. The use according to claim 3, wherein the COC comprising an equivalent effective amount of DRSP and another estrogen is a COC comprising an equivalent effective amount of DRSP and ethinyl-estradiol (EE).

5. The use according to any one of claims 1 to 4, wherein the one or more adverse effects of DRSP consists of a reduction of free testosterone blood plasma concentration associated with the use of a COC comprising an equivalent effective amount of DRSP and another estrogen, preferably a COC comprising an equivalent effective amount of DRSP and ethinyl-estradiol (EE) in a subject.

6. The use according to any one of claims 1 to 5, wherein the reduction of free testosterone blood plasma concentration is reduced by 10%, preferably by 15%, more preferably by 20%, in said subject using said COC when compared to a subject using a COC comprising an equivalent effective amount

of DRSP and another estrogen, preferably a COC comprising an equivalent effective amount of DRSP and ethinyl-estradiol (EE).

7. The use according to any one of claims 1 to 6, wherein the free testosterone blood plasma concentration is at least 25%, preferably at least 40%, more preferably at least 50% of a baseline value, wherein said baseline value is the free testosterone blood plasma concentration in said subject before using a COC comprising drospirenone.

8. The use according to any one of claims 1 to 7, wherein the free testosterone blood plasma concentration is at least 0.09 ng/dL, preferably at least 0.20 ng/dL in said subject when using said COC.

9. The use according to any one of claims 1 to 4, wherein the one or more adverse effects of DRSP consist of a QT interval prolongation by at least 5 milliseconds associated with the use of a COC comprising drospirenone in a subject, preferably wherein a QT interval is considered prolonged by at least 5 milliseconds when the time between the start of the Q wave and the end of the T wave in an electrocardiogram of a subject is prolonged by at least 5 milliseconds when compared to the QT interval of said subject prior to using a COC comprising drospirenone.

10. The use according to claim 9, wherein said risk for said subject to experience QT interval prolongation by at least 5 milliseconds is reduced by 10%, preferably by 25%, preferably by 50%, more preferably by 90%, or 100%, in said subject using said composition when compared to a subject using a COC comprising ethinylestradiol as estrogenic component and an equivalent effective amount of drospirenone.

11. The use according to claim 9 or 10, wherein the mean QT interval prolongation in a subject using said composition is 20%, preferably 35%, more preferably 50% shorter than a subject using a COC comprising an equivalent effective amount of DRSP and another estrogen, preferably a COC comprising an equivalent effective amount of DRSP and ethinyl-estradiol (EE).

12. The use according to any one of claims 9 to 11, wherein said composition has reduced estrogenic-related effects on the QT interval when compared to a subject using a COC comprising an equivalent effective amount of DRSP and another estrogen, preferably a COC comprising an equivalent effective amount of DRSP and ethinyl-estradiol (EE).

13. The use according to any one of claims 1 to 4, wherein the one or more adverse effects of DRSP consists of an increase in C-reactive protein blood plasma concentration associated with the use of a COC comprising drospirenone in a subject.

14. The use according to claim 13, wherein said C-reactive protein blood plasma concentration level is considered elevated when said concentration is 10% higher, preferably 20% higher, preferably

30% higher than a baseline value, wherein said baseline value is the C-reactive protein blood plasma concentration in said subject before using a COC comprising drospirenone.

15. The use according to claim 13 or 14, wherein the C-reactive protein blood plasma concentration is less than 2,00 mg/L, preferably less than 1,75 mg/L, more preferably less than 1,50 mg/L in said subject when using a COC comprising drospirenone.

16. The use according to any one of claims 1 to 15, wherein the composition is administered in periodic cycles, wherein said cycle comprises an administration-free interval of 7 days, preferably an administration-free interval of 4 days.

17. The use according to any one of claims 1 to 16, wherein a single dosage unit of the composition comprises about 3 mg drospirenone and about 15 mg of the estetrol component.