

CLAIMS

1. An amount of between 10 mg and 20 mg of estetrol as the estrogenic component of a daily active dosage unit in a combined oral contraceptive (COC) having drospirenone (DRSP) as progestogenic component in an amount of between 1 mg to 5 mg for use in providing the following pharmacokinetic profile for drospirenone in blood plasma when administered daily:
 - (i) a geometric mean AUC_{0-24} of drospirenone between about 150 and about 1000 ng.h/ml; and/or
 - (ii) a geometric mean C_{max} of drospirenone between about 10 ng/ml and 100 ng/ml.
2. An amount of between 10 mg and 20 mg of estetrol for use according to claim 1, wherein said daily active dosage unit is provided in a contraceptive kit comprising one or more packaging units each comprising 21 to 28 of said daily active dosage units of the combined oral contraceptive (COC).
3. An amount of between 10 mg and 20 mg of estetrol for use according to claim 1, wherein said COC is used continuously in cycles of 21 to 28 daily active dosage units of said COC.
4. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 1 to 3, wherein one or more adverse effects of DRSP are reduced compared to a subject under use of a COC comprising an equivalent effective amount of DRSP and another estrogen.
5. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 2 to 4, 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).
6. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 2 to 5, wherein the one or more adverse effects of DRSP comprise or consist of a decrease of free testosterone in blood plasma 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.
7. An amount of between 10 mg and 20 mg of estetrol for use according to claim 6, wherein the free testosterone decrease 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).
8. An amount of between 10 mg and 20 mg of estetrol for use according to claims 6 or 7, wherein the free testosterone blood plasma concentration level is at least 25%, preferably at least 40%, more preferably at least 50% of a baseline value, wherein said baseline value is the free blood plasma testosterone expression level in said subject before using a COC comprising drospirenone.

9. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 6 to 8, wherein the free testosterone concentration is at least 0.09 ng/dL, preferably at least 0.20 ng/dL in said subject when using said COC.
10. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 2 to 5, wherein the one or more adverse effects of DRSP comprise or consist of a risk of a prolonged QT interval associated with the use of a COC comprising drospirenone in a subject, preferably wherein a QT interval is considered prolonged 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.
11. An amount of between 10 mg and 20 mg of estetrol for use according to claim 10, wherein said risk for said subject to experience QT interval prolongation is reduced by 10%, preferably by 25%, preferably by 50%, more preferably by 90%, or 100%, in said subject using said COC when compared to a subject using a COC comprising ethinylestradiol as estrogenic component and an equivalent effective amount of drospirenone.
12. An amount of between 10 mg and 20 mg of estetrol for use according to claim 10 or 11, wherein the mean QT interval prolongation in a subject using said COC 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).
13. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 10 to 12, wherein said COC 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).
14. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 2 to 5, wherein the one or more adverse effects of DRSP comprise or consist of elevated C-reactive protein blood plasma concentration levels associated with the use of a COC comprising drospirenone in a subject.
15. An amount of between 10 mg and 20 mg of estetrol for use according to claim 14, wherein said C-reactive protein blood plasma concentration level is considered elevated when said level 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 level in said subject before using a COC comprising drospirenone.

16. An amount of between 10 mg and 20 mg of estetrol for use according to claim 14 or 15, wherein the C-reactive protein blood plasma concentration level 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.
- 5 17. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 1 to 16, wherein the COC is administered in periodic cycles, wherein said cycle comprises an administration-free interval of 7 days, preferably an administration-free interval of 4 days.
18. An amount of between 10 mg and 20 mg of estetrol for use according to any one of claims 1 to 17, wherein a single dosage unit of the COC comprises about 15 mg drospirenone and about 3 mg of
10 an estetrol component.
19. A method of reducing the pharmacokinetic profile for drospirenone in blood plasma of a subject using a combined oral contraceptive (COC) comprising drospirenone as progestogenic component in an amount of between 1 mg to 5 mg when administered daily to:
- (i) a geometric mean AUC_{0-24} of drospirenone between about 150 and about 1000 ng.h/ml; and/or
15 (ii) a geometric mean C_{max} of drospirenone between about 10 ng/ml and 100 ng/ml;
- said method comprising administering an amount of between 10 mg and 20 mg of estetrol as the estrogenic component of said combined oral contraceptive.
20. The method according to claim 19, wherein said subject is using said COC continuously in cycles of 21 to 28 daily active dosage units of said COC.
- 20 21. The method according to claim 19 or 20, wherein one or more adverse effects of DRSP are reduced compared to a subject under use of comprising a COC having an equivalent effective amount of DRSP and another estrogen.
22. The method according to any one of claims 19 to 21, wherein the COC comprising an equivalent effective amount of DRSP and another estrogen is a COC comprising an equivalent effective amount
25 of DRSP and ethinyl-estradiol (EE).
23. The method according to any one of claims 19 to 22, wherein the one or more adverse effects of DRSP comprises or consist of a decrease of free testosterone in blood plasma 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.
- 30 24. The method according to any one of claims 19 to 23, wherein the free testosterone decrease 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).

25. The method according to any one of claims 19 to 24, wherein the free testosterone blood plasma concentration level is at least 25%, preferably at least 40%, more preferably at least 50% of a baseline value, wherein said baseline value is the free blood plasma testosterone expression level in said subject before using a COC comprising drospirenone.

26. The method according to any one of claims 19 to 25, wherein the free testosterone concentration is at least 0.09 ng/dL, preferably at least 0.20 ng/dL in said subject when using said COC.

27. The method according to any one of claims 19 to 22, wherein the one or more adverse effects of DRSP comprise or consist of a risk of a prolonged QT interval associated with the use of a COC comprising drospirenone in a subject, preferably wherein a QT interval is considered prolonged 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.

28. The method according to claim 27, wherein said risk for said subject to experience QT interval prolongation is reduced by 10%, preferably by 25%, preferably by 50%, more preferably by 90%, or 100%, in said subject using said COC when compared to a subject using a COC comprising ethinylestradiol as estrogenic component and an equivalent effective amount of drospirenone.

29. The method according to claim 27 or 28, wherein the mean QT interval prolongation in a subject using said COC 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).

30. The method according to any one of claims 27 to 29, wherein said COC 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).

31. The method according to any one of claims 19 to 22, wherein the one or more adverse effects of DRSP comprise or consist of elevated C-reactive protein blood plasma concentration levels associated with the use of a COC comprising drospirenone in a subject.

32. The method according to claim 31, wherein said C-reactive protein blood plasma concentration level is considered elevated when said level 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 level in said subject before using a COC comprising drospirenone.

33. The method according to claim 31 or 32, wherein the C-reactive protein blood plasma concentration level 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.

34. The method according to any one of claims 31 to 33, wherein the COC is administered in periodic cycles, wherein said cycle comprises an administration-free interval of 7 days, preferably an administration-free interval of 4 days.

35. The method according to any one of claims 31 to 34, wherein a single dosage unit of the COC comprises about 15 mg drospirenone and about 3 mg of an estetrol component.

36. A composition comprising estetrol for use in reducing the bioavailability of DRSP in a subject under use of a combined oral contraceptive comprising DRSP.

37. The estetrol composition for use according to claim 36, wherein said estetrol functions as the estrogenic component of said combined oral contraceptive and DRSP functioning as the progestogenic component.

38. The estetrol composition for use according to claim 36 or 37, for use in reducing side effects of DRSP in a subject under continuous use of a combined oral contraceptive comprising DRSP.

39. The estetrol 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.

40. Estetrol for use in lowering the steady state bioavailability of DRSP in a combined oral contraceptive (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.

41. Estetrol for use in lowering the peak blood plasma concentration of DRSP in subjects continuously using a combined oral contraceptive (COC) comprising DRSP.

42. A method for reducing the risk of adverse effects of DRSP in a subject under a continuous regimen of a combined oral contraceptive (COC) comprising DRSP, comprising the step of providing a COC comprising DRSP as the progestogenic component and estetrol as the estrogenic component.

43. A combined oral contraceptive (COC) comprising estetrol and DRSP for use in reducing side effects of DRSP associated with the continuous use of a combined oral contraceptive comprising

DRSP, wherein the dosage-regime is applied for multiple periodic cycles, preferably comprising the application of 21 to 28 daily dosage units of COC comprising the active ingredients.

44. The COC comprising estetrol and DRSP for use according to claim 43, wherein said use is interrupted between the different periodic cycles for a period of 4 to 7 days, optionally by providing placebo dosage units not comprising the active ingredients of the combined oral contraceptive (COC), or simply by not taking any pills for those 4 to 7 days.

45. The COC comprising estetrol and DRSP for use according to claim 43 or 44, wherein 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.

46. Use of estetrol for the manufacture of a medicament for the prevention or treatment of adverse effect attributable to the use of DRSP in a combined oral contraceptive (COC).

47. Use of estetrol for the manufacture of a composition (i.e. medicament or contraceptive) for the prevention or treatment of QT interval prolongation in subjects using a combined oral contraceptive (COC) comprising DRSP .

48. Use of estetrol 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 combined oral contraceptive (COC) comprising DRSP .

49. Use of estetrol 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 combined oral contraceptive (COC) comprising DRSP.