WO2018/024912 and WO2018/065076 disclose the use of estetrol to alleviate the symptoms of dysmenorrhea. These patent applications are silent about the reduction of blood clot risk. Table 7 in these patent applications present the same clinical data as Table 1 of the Kluft at al. publication, although in a slightly different manner: while the Kluft at al. publication presents median values (expressed as percentage of the baseline value, taken as 100%), the patent applications present mean values (percentage changes).

There thus remains a need for a contraceptive approach which provides a better safety profile than currently available COCs, and in particular which displays a lower risk of thromboembolic events. This is especially critical in at-risk populations, such as first-ever users; switchers/re-starters with a break of >4 weeks; and women with increased baseline risk for VTE due to one or more major risk factors (such as, but not limited to, BMI>30, older age, and positive personal and/or family history).

Summary

The present disclosure relates to a contraceptive method with reduced cardiovascular effects, comprising administering to a female mammal an effective amount of an estetrol component in combination with a progestogenic component.

In one example of the disclosure, the number, frequency and/or severity of VTE events is reduced, compared to other contraceptive methods.

In a particular example, the risk of VTE during the contraceptive method of the disclosure is similar to the VTE risk during use of a CHC based on levonorgestrel, norgestimate or norethisterone.

In a preferred example, the risk of VTE during the contraceptive method of the disclosure is lower than the VTE risk during use of a CHC based on levonorgestrel, norgestimate or norethisterone.

In one example of the disclosure, the number, frequency and/or severity of pulmonary embolism events is reduced, compared to other contraceptive methods.

In another example of the disclosure, the number, frequency and/or severity of deep venous thrombosis (DVT) events is reduced, compared to other contraceptive methods.

In another example of the disclosure, no haemostatic change that exceeds the boundaries of the normal range, as further defined herein, occurs upon administration of the compositions of the disclosure.

In yet another example, the method of the disclosure displays smaller "haemostatic changes" (as further defined herein) than a contraceptive method employing a 2nd, 3rd or 4th generation CHC. In a particularly preferred example, the disclosure displays smaller "haemostatic changes" than a contraceptive method employing a 2nd generation CHC.

In a further example, markers of coagulation and/or fibrinolysis markers display changes (by comparison with their levels before administration of any contraceptive composition) during the contraceptive method of the disclosure which are smaller than the changes observed with another contraceptive method.

In a particular example, markers of coagulation and/or fibrinolysis markers display smaller changes during the contraceptive method of the disclosure than during a contraceptive method using a 2nd, 3rd or 4th generation CHC. In a preferred example, markers of coagulation and/or fibrinolysis markers display smaller changes during the contraceptive method of the disclosure than during a contraceptive method using a 2nd generation CHC.

In one example of the disclosure, an effective amount of an estetrol component is used in a combined oral contraceptive composition which uses drospirenone as the progestogenic component, in order to reduce the risk of blood clots associated with the use of drospirenone.

In another example of the disclosure, an effective amount of an estetrol component is used in a combined oral contraceptive composition which uses drospirenone as the progestogenic component, in order to reduce the risk of blood clots associated with the use of a combined oral contraceptive composition which includes drospirenone.

In all these aforementioned examples, the risk of blood clots is advantageously reduced to less than 8, preferably less than 7, more preferably less than 6, even more preferably less than 5, yet even more preferably less than 4 per 10,000 women using said contraceptive during one year.

In one example of the disclosure, the method involves the administration of an effective amount of an estetrol component and of a progestogenic component.

In some examples of the disclosure, the estetrol and the progestogenic components are included in a single dosage unit. In further examples, the dosage unit is a daily dosage unit.

In further examples, the progestogenic component is drospirenone and that component is used at a daily dose of from 0.5 mg to 10 mg, preferably at a daily dose of from 1 mg to 4 mg.

In yet further examples, the estetrol component is used at a daily dose of from 1 mg to 40 mg, preferably at a daily dose of from 5 mg to 25 mg, even more preferably at a daily dose of from 10 mg to 20 mg. In particular examples, the estetrol component is estetrol monohydrate.

In one aspect, the disclosure relates to use of a composition comprising from 15 mg to 20 mg estetrol and from 1 to 4 mg drospirenone in the manufacture of a medicament for oral contraception, wherein said composition is to be administered to a subject, wherein said composition does not result in haemostatic changes exceeding the boundaries of the normal haemostatic range in said subject such that the number of venous thromboembolism (VTE) cases is less than 5 per 10,000 women during one year, and wherein the normal haemostatic range is defined as the prediction interval that 95% of the population fall into and is determined based on any one or more of the following markers: Sex Hormone Binding Globulin (SHBG), free Tissue Factor Pathway Inhibitor (free TFPI), free and total Protein-S, Protein-S activity, Corticosteroid Binding Globulin (CBG), Ceruloplasmin, antithrombin III, Activated Protein C (APC) resistance, protein-

C activity, D-dimer, Prothrombin, Prothrombin fragment 1+2, Factor VII, Factor VIII, von Willebrand factor, Factor II, Plasminogen Activator Inhibitor type- I (PAI-I), tissue-type plasminogen (t-PA), plasminogen, E-selectin and fibrinogen.

In another aspect, the disclosure relates to use of a combined oral contraceptive in the manufacture of a medicament for avoiding haemostatic changes exceeding the boundaries of the normal haemostatic range in subjects using said combined oral contraceptive such that the number of venous thromboembolism (VTE) cases is less than 5 per 10,000 women during one year, wherein the combined oral contraceptive comprises from 15 mg to 20 mg estetrol and from 1 to 4 mg drospirenone, and wherein the normal haemostatic range is defined as the prediction interval that 95% of the population fall into and is determined based on any one or more of the following markers: Sex Hormone Binding Globulin (SHBG), free Tissue Factor Pathway Inhibitor (free TFPI), free and total Protein-S, Protein-S activity, Corticosteroid Binding Globulin (CBG), Ceruloplasmin, antithrombin III, Activated Protein C (APC) resistance, protein-C activity, D-dimer, Prothrombin, Prothrombin fragment 1+2, Factor VII, Factor VIII, von Willebrand factor, Factor II, Plasminogen Activator Inhibitor type- I (PAI-I), tissue-type Plasminogen (t-PA), plasminogen, E-selectin and fibrinogen.

In a specific embodiment of the disclosure, the estetrol component is estetrol monohydrate at a daily dose of about 15 mg and the progestogenic component is drospirenone at a daily dose of about 3 mg.

In the following numbered paragraphs 1 to 22, additional examples of the disclosure are described.

1. A composition for use in a contraceptive method in a female mammal, wherein said composition comprises an effective amount of an estetrol component.
2. The composition for use of paragraph 1 wherein said composition further comprises a progestogenic component.

15. A composition for use according to any one of the paragraphs 1-12 wherein the number of VTE cases is less than 15-20 VTE per 10,000 women during one year.
16. A composition for use according to paragraph 15 wherein the number of VTE cases is less than 15, preferably less than 13, more preferably less than 11, even more preferably less than 10 VTE per 10,000 women during one year.
17. A composition for use according to any one of the preceding paragraphs wherein the VTE risk is lower than the VTE risk associated with a 3rd generation or with a 4th generation COC.
18. A composition for use according to any one of the preceding paragraphs wherein the VTE risk is lower than the VTE risk associated with a 2nd generation COC.
19. A composition for use according to paragraph 17 or 18 wherein the profile of side effects other than VTE is better than the profile of side effects associated with a 2nd generation COC.
20. A composition for use according to any one of the preceding paragraphs wherein the relative venous thrombosis risk, by comparison to a woman not using COCs, is lower than 4.5, preferably lower than 4.0, more preferably lower than 3.5, even more preferably lower than 3.2, yet even more preferably lower than 3.0.
21. A composition for use according to any one of the preceding paragraphs wherein the percentage of subjects in the high risk category for thrombosis, defined as subjects having an odds ratio of 2 or above for thrombosis risk compared to subjects not using COCs, represents less than 40%, preferably less than 35%, more preferably less than 30%, even more preferably less than 25%, yet even more preferably less than 20%, of the total population using said composition.
22. A composition for use according to any one of the preceding paragraphs wherein the composition is administered to a woman who is a first-ever user, or a woman who is a switcher or a re-starter with a break of >4 weeks, or a woman with increased baseline risk for VTE due to one or more major risk factors selected from BMI>30, older age, and positive personal and/or family history.

In the following numbered paragraphs 31 to 52, additional examples of the disclosure are described.

In the following numbered paragraphs 61 to 82, additional examples of the disclosure are described.

61. Use of an effective amount of an estetrol component in the manufacture of a composition for a contraception method in a female mammal.
62. Use of paragraph 61 wherein said composition further comprises a progestogenic component.
63. Use of paragraph 61 or 62 wherein said method results in the reduction of one or more of the number, the frequency and the severity of VTE events compared to other contraceptive methods.
64. Use of paragraph 63 wherein said progestogenic component is drospirenone.
65. Use according to any one of paragraphs 61-64 wherein the estetrol component is used at a daily dose of from 1 mg to 40 mg, preferably at a daily dose of from 5 mg to 25 mg.
66. Use of paragraph 64 wherein drospirenone is used at a daily dose of from 0.5 mg to 10 mg, preferably at a daily dose of from 1 mg to 4 mg.
67. Use according to any one of paragraphs 61-66 wherein the method is a combined method with an administration-free interval of about 7 days, preferably with an administration-free interval of about 4 days.
68. Use according to any one of paragraphs 61-67 wherein the estetrol component is estetrol, preferably estetrol monohydrate.
69. Use according to paragraph 68 wherein the estetrol component is used at a daily dose of about 15 mg of estetrol.
70. Use according to paragraph 69 wherein the drospirenone is used at a daily dose of about 3 mg.
71. Use according to any of the preceding paragraphs wherein the composition is formulated as an oral dosage unit.
72. Use according to paragraph 71 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.
73. Use according to any one of paragraphs 63-72 wherein the risk of blood clots occurrence is less than 12, preferably less than 11, more preferably less than 10, even

In the following numbered paragraphs 91 to 105, additional examples of the disclosure are described.

91. A contraceptive method for a female mammal, which comprises administration of a combined oral contraceptive comprising an effective amount of an estetrol component as the estrogenic component and an effective amount of drospirenone as the progestogenic component, wherein the estetrol component reduces the risk of thromboembolism associated with the use of drospirenone.
92. The contraceptive method of paragraph 91, wherein said risk of thromboembolism is reduced to less than 8, preferably less than 7, more preferably less than 6, even more preferably less than 5, yet even more preferably less than 4 per 10,000 women using said contraceptive during one year.
93. The contraceptive method of paragraphs 91 or 92, wherein the estetrol component is used at a daily dose of from 1 mg to 40 mg, preferably at a daily dose of from 5 mg to 25 mg.
94. The contraceptive method of any of paragraphs 91-93 wherein drospirenone is used at a daily dose of from 0.5 mg to 10 mg, preferably at a daily dose of from 1 mg to 4 mg.
95. The contraceptive method of any one of paragraphs 91-94 wherein the administration method is a combined method with an administration-free interval of about 7 days, preferably with an administration-free interval of about 4 days.
96. The contraceptive method of any one of paragraphs 91-95 wherein the estetrol component is estetrol, preferably estetrol monohydrate.
97. The contraceptive method of paragraph 96 wherein estetrol is used at a daily dose of about 15 mg of estetrol.
98. The contraceptive method of paragraph 97 wherein drospirenone is used at a daily dose of about 3 mg.
99. The contraceptive method of any of the preceding paragraphs wherein the contraceptive is formulated as an oral dosage unit.
100. The contraceptive method according to paragraph 99 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.

101. The contraceptive method according to any one of the preceding paragraphs wherein the VTE risk is lower than the VTE risk associated with a 2nd generation COC.

102. The contraceptive method according to paragraphs 100 or 101 wherein the profile of side effects other than VTE is better than the profile of side effects associated with a 2nd generation COC.

103. The contraceptive method according to any one of the preceding paragraphs wherein the relative venous thrombosis risk, by comparison to a woman not using COCs, is lower than 3.5, preferably lower than 3.2, more preferably lower than 3.0, even more preferably lower than 2.5, yet even more preferably lower than 2.0.

104. The contraceptive method according to any one of the preceding paragraphs wherein the percentage of subjects in the high risk category for thrombosis, defined as subjects having an odds ratio of 2 or above for thrombosis risk compared to subjects not using COCs, represents less than 40%, preferably less than 35%, more preferably less than 30%, even more preferably less than 25%, yet even more preferably less than 20%, of the total population using said composition.

105. The contraceptive method according to any one of the preceding paragraphs wherein the composition is administered to a woman who is a first-ever user, or a woman who is a switcher or a re-starter with a break of >4 weeks, or a woman with increased baseline risk for VTE due to one or more major risk factors selected from BMI>30, older age, and positive personal and/or family history.

In the following numbered paragraphs 111 to 125, additional examples of the disclosure are described.

111. Use of an effective amount of an estetrol component as the estrogenic component in the manufacture of a combined oral contraceptive for a contraception method in a female mammal wherein an effective amount of drospirenone is the progestogenic component, and wherein the estetrol component reduces the risk of thromboembolism associated with the use of drospirenone.

112. Use of paragraph 111 wherein said risk of thromboembolism is reduced to less than 8, preferably less than 7, more preferably less than 6, even more preferably less than 5, yet even more preferably less than 4 per 10,000 women using said contraceptive during one year.

Claims

1. Use of a composition comprising from 15 mg to 20 mg estetrol and from 1 to 4 mg drospirenone in the manufacture of a medicament for oral contraception, wherein said composition is to be administered to a subject, wherein said composition does not result in haemostatic changes exceeding the boundaries of the normal haemostatic range in said subject such that the number of venous thromboembolism (VTE) cases is less than 5 per 10,000 women during one year, and wherein the normal haemostatic range is defined as the prediction interval that 95% of the population fall into and is determined based on any one or more of the following markers: Sex Hormone Binding Globulin (SHBG), free Tissue Factor Pathway Inhibitor (free TFPI), free and total Protein-S, Protein-S activity, Corticosteroid Binding Globulin (CBG), Ceruloplasmin, antithrombin III, Activated Protein C (APC) resistance, protein-C activity, D-dimer, Prothrombin, Prothrombin fragment 1+2, Factor VII, Factor VIII, von Willebrand factor, Factor II, Plasminogen Activator Inhibitor type- I (PAI-I), tissue-type plasminogen (t-PA), plasminogen, E-selectin and fibrinogen.

2. The use according to claim 1, for preventing risk increase of developing VTE in a subject compared to other combined oral contraceptives (COCs).

3. Use of a combined oral contraceptive in the manufacture of a medicament for avoiding haemostatic changes exceeding the boundaries of the normal haemostatic range in subjects using said combined oral contraceptive such that the number of venous thromboembolism (VTE) cases is less than 5 per 10,000 women during one year, wherein the combined oral contraceptive comprises from 15 mg to 20 mg estetrol and from 1 to 4 mg drospirenone, and wherein the normal haemostatic range is defined as the prediction interval that 95% of the population fall into and is determined based on any one or more of the following markers: Sex Hormone Binding Globulin (SHBG), free Tissue Factor Pathway Inhibitor (free TFPI), free and total Protein-S, Protein-S activity, Corticosteroid Binding Globulin (CBG), Ceruloplasmin, antithrombin III, Activated Protein C (APC) resistance, protein-C activity, D-dimer, Prothrombin, Prothrombin fragment 1+2, Factor VII, Factor VIII,

von Willebrand factor, Factor II, Plasminogen Activator Inhibitor type- I (PAI-I), tissue-type Plasminogen (t-PA), plasminogen, E-selectin and fibrinogen.

4. The use according to claim 3, for preventing risk increase of developing VTE associated with the use of COC's in subjects using the combined oral contraceptive.

5. The use according to any one of claims 1 to 4, wherein said haemostatic change is determined based on a change in level of Protein-S or free TFPI when compared to the normal haemostatic range.

6. The use according to any one of claims 1 to 5, wherein said haemostatic change is measured after one cycle of treatment, after two cycles of treatment or after three cycles of treatment.

7. The use according to any one of claims 1 to 6, wherein said oral contraceptive comprises about 15 mg estetrol.

8. The use according to any one of claims 1 to 7, wherein said oral contraceptive comprises about 20 mg estetrol.

9. The use according to any one of claims 1 to 8, wherein said oral contraceptive comprises about 3 mg drospirenone.

10. The use according to any one of claims 1 to 9, wherein said estetrol is estetrol monohydrate.

11. The use according to any one of claims 1 to 10, wherein said composition is to be administered during at least 21 days, or during 24 days, respectively followed by an administration-free period of about 7 to 4 days.