and 10 mg) to be suitable for the management of VMS. Further, the skilled person learns that a daily dose of 2 mg estetrol is as effective as a daily dose of 10 mg estetrol at decreasing the number of hot flushes per day (see for example Figure 3 in Coelingh Bennink et al., Maturitas, 2016). In addition, the publication teaches the skilled person that the 2 mg daily dose does not alter endometrial thickness while the 10 mg daily dose has an important effect on endometrial thickness (see for example Figure 2 in Coelingh Bennink et al., 2016). The skilled person would thus conclude that the Minimal Effective Dose of estetrol for the treatment of VMS is 2 mg per day.

Summary

Against this background, the present inventors have now surprisingly found that the Minimal Effective Dose of estetrol for the alleviation of VMS in perimenopausal and postmenopausal women is of about 15 mg daily.

The determination of the Minimal Effective Dose indeed revolves around a number of parameters which take into account not only the mean number of VMS per day (as was done by Coelingh Bennink et al in Maturitas, 2016), but also the severity of VMS, and also a weekly weighted score, as further defined herein.

Thus, in terms of efficacy, it was surprisingly found that a daily dose of 15 mg was required to obtain a definite effect on VMS.

Furthermore, it was observed by the present inventors that several side effects of the treatment, as reflected for example in the number of treatment-emergent adverse events (TEAEs), or in the number of patients leaving the study in each group, or in the number of biopsies which had to be performed in each group, tend to reach a plateau at around 10 mg per day, and do not worsen when the dose is further increased. Surprisingly, some of these parameters in fact regress from 10 mg to 15 mg daily, thus indicating that the adverse events could be more bearable when the dose is higher than 10 mg per day.

Based on this surprising finding, and on measurements performed when a 20 mg and a 30 mg daily doses are administered, the present inventors have thus come to the unexpected conclusion that an optimal daily dose of estetrol for alleviation of VMS in postmenopausal women is found in the range of 15 mg to 25 mg. This range of doses indeed allows statistically significant effects on VMS to be observed, as is shown in the examples, while maintaining the treatment side effects within an acceptable window.

In one aspect, there is provided use of a composition in the manufacture of a medicament for the alleviation of menopause-associated symptoms, wherein said composition comprises an estetrol component and wherein said composition is to be administered at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

In another aspect, there is provided a packaging unit comprising at least 21, preferably at least 28, containers for holding separately packaged and individually removable daily solid oral dosage forms, wherein each container comprises at least one daily solid oral dosage form comprising from about 15 mg to about 25 mg of estetrol.

In the following numbered paragraphs 1 to 14, examples of the disclosure are described.

1. A composition for use in alleviating menopause-associated symptoms, wherein said composition comprises an estetrol component and wherein said composition is administered at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

2. A composition for use in alleviating vasomotor symptoms selected from hot flashes, sweating attacks, night sweats, chills, increased perspiration, palpitations and combinations thereof,

11. A composition for use according to any one of paragraphs 7-10 wherein said second composition comprising a progestogenic component or bazedoxifene is the same as the composition comprising the estetrol component.

12. A composition for use according to any one of paragraphs 1-11 wherein the estetrol component is estetrol, preferably estetrol monohydrate.

13. A composition for use according to any of the preceding paragraphs wherein the composition is formulated as an oral dosage unit.

14. The composition for use according to paragraph 13 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.

In the following numbered paragraphs 15 to 28, additional examples of the disclosure are described.

15. A method of alleviating menopause-associated symptoms which comprises administration of a composition comprising an estetrol component at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

16. A method of alleviating vasomotor symptoms selected from hot flashes, sweating attacks, night sweats, chills, increased perspiration, palpitations and combinations thereof, which comprises administration of a composition comprising an estetrol component at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

17. A method of alleviating emotional aspects of the menopausal transition selected from depression, irritability, mood changes, insomnia, sleep disturbance, anxiety, nervous tension and combinations thereof, which comprises administration of a composition comprising an estetrol component at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

18. A method of alleviating physiological aspects of the menopausal transition selected from joint pain, loss of bone density, urinary tract infections, urinary incontinence, dryness of the vagina, uterine prolapse, changes in skin texture, weight gain, dyspareunia, cardiovascular diseases, diabetes and combinations thereof, which comprises administration of a composition comprising an estetrol component at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

19. A method of reducing VMS frequency, VMS severity, hot flush weekly weighted score, dryness of the vagina, dyspareunia and combinations thereof, or of improving Quality of Life according to the MRS and/or the MENQOL questionnaires, which comprises administration of a

composition comprising an estetrol component at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

20. The method according to any one of paragraphs 15-19 above wherein the composition is administered daily for at least 1, at least 2, at least 4, at least 6, at least 12 weeks.

21. The method according to any one of paragraphs 15-20 wherein a second composition comprising a progestogenic component is additionally administered.

22. The method according to paragraph 21 wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone.

23. The method according to paragraph 22 wherein progesterone is administered at a daily dose of from 50 mg to 200 mg.

24. The method according to any one of paragraphs 15-20 wherein a second composition comprising bazedoxifene is additionally administered.

25. The method according to any one of paragraphs 21-24 wherein said second composition comprising a progestogenic component or bazedoxifene is the same as the composition comprising the estetrol component.

26. The method according to any one of paragraphs 15-25 wherein the estetrol component is estetrol, preferably estetrol monohydrate.

27. The method according to any of the preceding paragraphs wherein the composition is formulated as an oral dosage unit.

28. The method according to paragraph 27 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.

In the following numbered paragraphs 29 to 42, additional examples of the disclosure are described.

29. Use of an effective amount of an estetrol component in the manufacture of a composition for alleviating menopause-associated symptoms, wherein the estetrol component is used at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

30. Use of an effective amount of an estetrol component in the manufacture of a composition for alleviating vasomotor symptoms selected from hot flashes, sweating attacks, night sweats,

40. The use according to any one of paragraphs 29-39 wherein the estetrol component is estetrol, preferably estetrol monohydrate.

41. The use according to any of the preceding paragraphs wherein the composition is formulated as an oral dosage unit.

42. The use according to paragraph 41 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.

In the following numbered paragraphs 43 to 50, additional examples of the disclosure are described.

43. A packaging unit comprising at least 14, preferably at least 21, even more preferably at least 28, containers for holding separately packaged and individually removable daily solid oral dosage forms, wherein each container comprises at least one daily solid oral dosage form comprising from about 15 mg to about 25 mg of estetrol.

44. The packaging unit according to paragraph 43, wherein the packaging unit additionally comprises at least 10, preferably 12, more preferably 14, additional containers for holding separately packaged and individually removable daily, preferably solid, oral dosage forms, wherein each additional container comprises at least one daily, preferably solid, oral dosage form comprising a progestogenic component.

45. The packaging unit according to paragraph 44, wherein each of the additional containers for holding the dosage forms comprising the progestogenic component are individually visually arranged next to a container holding a solid dosage form comprising estetrol when these two solid dosage forms have to be administered on the same day.

46. The packaging unit according to paragraphs 44 or 45, wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone.

47. The packaging unit according to paragraph 46, wherein said progestogenic component is progesterone and wherein each said additional containers comprises at least one daily oral dosage form comprising about 200 mg of progesterone.

48. The packaging unit according to paragraph 43, wherein the packaging unit additionally comprises the same number of additional containers for holding separately packaged and individually removable daily, preferably solid, oral dosage forms, wherein each additional

container comprises at least one daily, preferably solid, oral dosage form comprising a progestogenic component, preferably wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone, even more preferably wherein said progestogenic component is progesterone and wherein said additional container comprises at least one daily oral dosage form comprising about 100 mg of progesterone.

49. The packaging unit according to paragraph 43, wherein at least 10, preferably 12, more preferably 14, of said daily solid oral dosage forms additionally comprises a progestogenic component.

50. The packaging unit according to paragraph 43, wherein each said daily solid oral dosage form additionally comprises a progestogenic component.

The skilled person will understand that the examples described in numbered paragraphs 44 to 50 may equivalently be presented as a kit-of-parts containing a first packaging unit, e.g. a blister pack, containing the daily oral dosage units comprising the estetrol component, and a second, distinct, packaging unit, e.g. a second, distinct, blister pack, containing the daily oral dosage units comprising the progestogenic component.

The skilled person will additionally know that, within the scope of the present disclosure, each packaging unit, e.g. blister pack, may be numbered or otherwise marked.

Within the scope of the disclosure, each packaging unit may be a sealed blister pack with a cardboard, paperboard, foil plastic backing and enclosed in a suitable cover.

In a particular example of the disclosure the packaging unit comprises 28 containers or a multiple of 28 containers, such as 2 to 12 multiple of 28 containers.

Detailed description of the invention

Definitions

The term “estetrol component”, as used throughout this document, encompasses substances selected from the group consisting of estetrol, esters of estetrol wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; and combinations thereof. Even more preferably, the estetrol component is estetrol (including estetrol hydrates). Most preferably, the estetrol component contained in the dosage unit is estetrol monohydrate.

The term “estetrol” as used herein refers to 1,3,5 (10)-estratrien-3,15alpha,16alpha,17beta-tetrol or 15alpha-hydroxyestriol as well as hydrates of estetrol, e.g. estetrol monohydrate.

Claims

1. Use of a composition in the manufacture of a medicament for the alleviation of menopause-associated symptoms, wherein said composition comprises an estetrol component and wherein said composition is to be administered at a daily amount equivalent to from about 15 mg to about 25 mg of estetrol.

2. The use of a composition according to claim 1 wherein a second composition comprising a progestogenic component is additionally used.

3. The use of a composition according to claim 2 wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone.

4. The use of a composition according to claim 2 wherein progesterone is to be administered at a daily dose of from 50 mg to 200 mg.

5. The use of a composition according to claim 1 wherein a second composition comprising bazedoxifene is additionally used.

6. The use of a composition according to any of claims 2 to 5 wherein said second composition comprising a progestogenic component or bazedoxifene is the same as the composition comprising the estetrol component.

7. The use of a composition according to any one of claims 1 to 6 wherein the estetrol component is estetrol, preferably estetrol monohydrate.

8. The use of a composition according to any one of claims 1 to 7 wherein the composition is formulated as an oral dosage unit.

9. The use of a composition according to claim 8 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.

10. A packaging unit comprising at least 21, preferably at least 28, containers for holding separately packaged and individually removable daily solid oral dosage forms, wherein each container comprises at least one daily solid oral dosage form comprising from about 15 mg to about 25 mg of estetrol.

11. The packaging unit according to Claim 10, wherein the packaging unit additionally comprises at least 10, preferably 12, more preferably 14, additional containers for holding separately

packaged and individually removable daily, preferably solid, oral dosage forms, wherein each additional container comprises at least one daily, preferably solid, oral dosage form comprising a progestogenic component.

12. The packaging unit according to Claim 11, wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone.

13. The packaging unit according to Claim 12, wherein said progestogenic component is progesterone and wherein each said additional containers comprises at least one daily oral dosage form comprising about 200 mg of progesterone.

14. The packaging unit according to Claim 10, wherein the packaging unit additionally comprises the same number of additional containers for holding separately packaged and individually removable daily, preferably solid, oral dosage forms, wherein each additional container comprises at least one daily, preferably solid, oral dosage form comprising a progestogenic component, preferably wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone, even more preferably wherein said progestogenic component is progesterone and wherein said additional container comprises at least one daily oral dosage form comprising about 100 mg of progesterone.

15. The packaging unit according to Claim 10, wherein each said daily solid oral dosage form additionally comprises a progestogenic component.