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 vasomotor symptoms, wherein said composition is formulated as an oral dosage unit comprising 20 mg estetrol monohydrate and is to be orally administered once daily.

Claims

1. Use of a composition in the manufacture of a medicament for the alleviation of menopause-associated vasomotor symptoms, wherein said composition is formulated as an oral dosage unit comprising 20 mg estetrol monohydrate and is to be orally administered once daily.

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 3 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 claim 1 wherein the oral dosage unit is formulated to correspond to a daily dosage unit.

8. The use according to claim 7, wherein said daily dosage form is present in a packaging unit comprising at least 21, preferably at least 28, containers for holding separately packaged and individually removable daily solid oral dosage forms.

9. The use according to Claim 8, 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.

10. The use according to Claim 9, wherein said progestogenic component is selected from drospirenone, progesterone and dydrogesterone.

11. The use according to Claim 10, wherein said progestogenic component is progesterone and wherein each said additional container comprises at least one daily oral dosage form comprising 200 mg of progesterone.

12. The use according to Claim 8, 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 100 mg of progesterone.

13. The use according to Claim 8, wherein each said daily solid oral dosage form additionally comprises a progestogenic component.

14. Use of a packaging unit comprising at least 21, preferably at least 28, containers for holding separately packaged and individually removable daily solid oral dosage forms in the manufacture of a kit for the alleviation of menopause-associated vasomotor symptoms, wherein each container comprises at least one daily solid oral dosage form comprising 20 mg of estetrol monohydrate.