CONTRACEPTIVE PHARMACEUTICAL PREPARATION

Description

Field of the invention

The invention relates to a pharmaceutical composition comprising dienogest in an amount which on administration of the composition corresponds to a daily dose unit of 1.5 mg or 2.0 mg and comprising ethinylestradiol in an amount which on administration of the composition corresponds to a daily dose unit of 0.015 mg or 0.020 mg, together with one or more pharmaceutically acceptable carriers for at least 21 daily dose units.

The invention further relates to a pharmaceutical product for oral contraception comprising 1.5 mg of 17α-cyanomethyl-17-β-hydroxyestra-4,9-dien-3-one (dienogest) and 0.015 or 0.020 mg of 17α-ethinylestradiol (ethinylestradiol) or 2.0 mg of dienogest and 0.015 mg of ethinylestradiol, together with one or more pharmaceutically acceptable carriers for at least 21 daily dose units of a 28-day menstrual cycle.

General prior art

Oral contraceptive compositions consisting of a progestogen component and of an oestrogen component were marketed for the first time in the early 1960s. Three essential properties characterize the profile of the "contraceptive pill": contraceptive reliability, very good cycle control and a minimum of side effects. The contraceptive reliability derives primarily from the progestogen component. The effect of this is to inhibit gonadotropin release in the pituitary and to inhibit ovulation. In addition, the peripheral effect of the progestogen on the endometrium results in a reduced probability of implantation of the fertilized

ovum; on the cervix results in secretion of viscous secretion which reduces the sperm in the uterus. A peripheral effect on the fallopian tubes should also be noted.

The oestrogen component enhances the anovulatory effect of the progestogen and is responsible for acceptable cycle control. Since the introduction of hormonal contraceptives, research has been directed to developing products which, while the contraceptive reliability and cycle control remain good, reduces unwanted side effects such as, for example, arterial and venous thromboses and effects on carbohydrate and lipid metabolism. Such side effects are known in particular for first-generation oral contraceptives which comprised a higher content of progestogen and oestrogen than was necessary for contraception.

WO 98/004269 discloses inter alia the oral administration of a combination of 250 µg-4 mg of dienogest and 10 µg-20 µg of ethinylestradiol for contraception. In order to achieve the substantial reduction in the total contraceptive steroid administered per cycle, while retaining a good cycle control, the low-dose progestogen/oestrogen combination is administered for 23 to 25 days of a 28-day menstrual cycle. However, the patent does not disclose results and information proving that the inventive idea is also successful.

WO 01/015701 claims a pharmaceutical composition also for oral administration on 21 days of a 28-day menstrual cycle, which comprises drospirenone and ethinylestradiol, inter alia also in low dose, the drospirenone being present in micronized form. Particular attention is directed in this case to rapid release of the steroids.

It is known from the specialist and patent literature that steroidal active ingredients are metabolized by the cytochrome P 450 enzyme system which is also at the same time responsible for the breakdown of a number of

medicinal products. Certain medicinal products, such as barbiturates, antiepileptics and selected virostatics, induce this enzyme system and reduce the concentration of the steroid active ingredients in the blood. In order to compensate for this, it would really be necessary for the progestogen content to be increased or at least maintained, and not reduced, which induces the side effects identified above, however.

Detailed disclosure of the invention

The invention is based on the object of indicating a pharmaceutical composition based on dienogest and ethinylestradiol, in which the total steroidal dosage is reduced, at the same time the balance between dienogest and ethinylestradiol is retained, the contraceptive efficacy and a good cycle control is attained and side effects such as, for example, additional reduction in the active ingredient levels in the blood on concomitant intake of further medicinal products is compensated.

This object is achieved according to the invention by a pharmaceutical composition comprising dienogest in an amount which on administration of the composition corresponds to a daily dose unit of 1.5 mg or 2.0 mg and comprising ethinylestradiol in an amount which on administration of the composition corresponds to a daily dose unit of 0.015 mg or 0.020 mg, together with one or more pharmaceutically acceptable carriers for at least 21 daily dose units.

The object is also achieved according to the invention by a pharmaceutical product for oral contraception comprising 1.5 mg of 17α-cyanomethyl-17-β-hydroxyestra-4,9-dien-3one (dienogest) and 0.015 mg or 0.020 mg of 17α-ethinylestradiol (ethinylestradiol) or 2.0 mg of dienogest and 0.015 mg of ethinylestradiol, together

with one or more pharmaceutically acceptable carriers to form at least 21 daily dose units of a 28-day menstrual cycle.

It is clear in this connexion from the wording of Claim 2 that the pill users take the pill for at least 21 days and interpolate 7 pill-free days. The statement "21 days of a 28-day menstrual cycle" is to be equated in its significance and extent in the field of hormonal contraception with the statement "21 days of hormone pill + 7 pill-free days" in the field.

The dienogest/ethinylestradiol active ingredient combination is incorporated together with one or more pharmaceutically acceptable carriers or medicinal product carriers in the pharmaceutical product. Embodiments are pharmaceutical products in the form of tablet preparations. The pharmaceutical product in this case is a film-coated tablet is consisting of a tablet core with a dienogest content and of an active ingredient-containing film coating with a dienogest content and a total ethinylestradiol content.

In a particular embodiment of the pharmaceutical product according to the invention, there is delayed dissolution of the proportion of dienogest of at least 30%, preferably 50%, of dienogest from the tablet core after more than 30 min, and dissolution of the proportion of dienogest and of the total ethinylestradiol content of at least 75% in a maximum of 45 min, preferably 70% in 30 min, from the film coating, as determined by the dissolution test using water at 37°C as dissolution medium and a stirring speed of 50 rpm.

It is also conceivable that, together with the proportion of dienogest, there is delayed release of a proportion of ethinylestradiol from the total ethinylestradiol content, preferably from the tablet core.

The number of daily dose units in suitable embodiments

of the pharmaceutical product according to the invention can amount to 22, 23, 24 or 25 daily dose units, and the number of active ingredient-free daily dose units then amounts to 6, 5, 4 or 3 in the 28-day menstrual cycle.

It has been found that surprisingly the partial delayed dissolution (release) of the dienogest from the tablet preparations enables the dosage of the dienogest/ethinylestradiol active ingredient combination to be in the low range according to the invention.

The appended figure 1 shows curves according to the corresponding release profiles of a film-coated tablet with the total dose of 1.5 mg of dienogest and 0.015 mg of ethinylestradiol. The release of proportions of dienogest in two phases is clearly evident, i.e. a slow (delayed) release and a non-slow (rapid) release - in this regard, see the broken-line markings at 30 min and 45 min. It is furthermore evident further that after 30 min and 45 min have elapsed, the proportion of dienogest which has undergone slow (delayed) release is greater than 30%, preferably 50%, as already explained. A release behaviour of at least 75% of the active ingredient dose within 45 min, preferably 70% in 30 min, is called rapid release.

It has also emerged that the active ingredient combination in the pharmaceutical product according to the invention has, besides the contraception, antiandrogenic properties and can therefore be used for the prophylaxis and therapy of androgen-induced disorders, especially of acne.

It is possible to use the combination of 1.5 mg to 2.0 mg of dienogest and 0.015 mg to 0.020 mg of ethinylestradiol for producing a pharmaceutical product or for the preparation of a pharmaceutical composition according to the invention for inhibiting ovulation.

Contraceptive efficacy of formulations which comprise dienogest and ethinylestradiol.

In a randomized, open clinical study, 40 women between 18 and 35 years of age, who had given their written consent to take part in the study, were treated with 2 different formulations which contained dienogest and ethinylestradiol. The first formulation (A) corresponded to a combination of 2 mg of dienogest (release not delayed) and 0.02 mg of ethinylestradiol. The second formulation (B) consisted of a combination of 1.5 mg of dienogest (delayed release of 50% = 0.75 mg) and 0.02 mg of ethinylestradiol.

The trial included a pretreatment cycle (washout phase), 3 treatment cycles and an after-treatment cycle (follow-up phase).

At fixed times (before the start of the first treatment cycle, at the end of the third treatment cycle), various biochemical and function-testing investigations are carried out.

To detect the ovulation-inhibiting effect, FSH, LH, oestradiol, progesterone, "spinnbarkeit" and ferning were investigated. Follicle maturation was examined by means of an ultrasound investigation. In addition, SHBG, CBG, total testosterone, triglycerides, cholesterol, HDL, LDL, glucose in serum were determined, and blood pressure, heart rate, body weight and bleeding behaviour were recorded.

The results of the study prove that both formulations reliably inhibit ovulation, as proved by the fall in LH, FSH, progesterone and estradiol during the treatment cycles. Follicle growth was detectable in both groups by the accompanying ultrasound investigation, that led, however, to follicle rupture and thus to ovulation in no participant in the study. So-called LUFs (luteinized unruptured follicles), which represent evidence that follicle maturation has taken place, but ovulation has not, were detectable in treatment cycle 2 and 3 in 3 women treated with formulation A. The increases in SHBG and CB were

comparable in the two treatment groups. The "spinnbarkeit" and ferning parameters which are principally influenced by the progestogen component of the products showed a tendency to be reduced more in the group treated with formulation B than in the comparison group. However, the difference did not reach statistical significance. The increase in HDL-cholesterol and the fall in LDL-cholesterol was significantly greater in treatment group B than in group A. Triglycerides and total cholesterol showed comparable changes in the two groups. The glucose tolerance remained substantially unaffected in the two groups. Total testosterone decreased in a comparable way and significantly in both treatment groups. The subjective and objective tolerability of formulation B was assessed as more favourable. Less irregular bleeding occurred, especially in the first treatment cycle. The intensity of the regular progestogen withdrawal bleeding (in the pill break) was also less. In addition, women treated with formulation B reported fewer premenstrual symptoms (headaches, abdominal pain). No differences were found between the groups and in the time course in relation to blood pressure, heart rate and body weight.

The study which was carried out showed that both products reliably prevented ovulation in all the volunteers. There was found to be a tendency for there to be enhanced peripheral anticontraceptive effects with formulation B. A few unfavourable side effects (bleeding irregularities, premenstrual symptoms) occurred significantly less often with formulation B. A more favourable lipid profile was found for formulation B.

The results show that a delayed dissolution (release) of dienogest enables the dosage both of dienogest and of ethinylestradiol to be low (formulation B), i.e. the total steroidal dosage is reduced and, at the same time, the requirement for a balance between dienogest

and ethinylestradiol is met. Likewise, good contraceptive efficacy and cycle control is achieved, and such side effects such as, for example, additional reduction in the active ingredient levels in the blood on concomitant intake of further medicinal products is compensated.

On reduction of the progestogen (dienogest) content with the same estrogen (ethinylestradiol) content different effects it is to be expected from the outset that the contraceptive efficacy will deteriorate, good cycle control will not be achieved, and the side effects will intensify, because a shift in the balance between dienogest and ethinylestradiol will be expected.
Contrary to this view, the results show that a delayed dissolution (release) of dienogest enables the dosage both of dienogest and of ethinylestradiol to be low (formulation B = 1.5 mg), i.e. the total steroidal dosage is reduced and, at the same time, the requirement for a balance between dienogest and ethinylestradiol is met. Likewise, good contraceptive efficacy and cycle control is achieved, and such side effects such as, for example, additional reduction in the active ingredient levels in the blood on concomitant intake of further medicinal products is compensated.
Formulation A = 2.0 mg of dienogest having the same ethinylestradiol content as in formulation B = 0.02 mg of ethinylestradiol, which comprises a low dosage of ethinylestradiol compared with conventional products, also shows a detectable ovulation-inhibiting effect, but not so comprehensive as formulation B which has a lower dose both in the dienogest content and in the ethinylestradiol content.

Claims

1. Pharmaceutical composition comprising dienogest in an amount which on administration of the composition corresponds to a daily dose unit of 1.5 mg or 2.0 mg and comprising ethinylestradiol in an amount which corresponds to a daily dose unit of 0.015 mg or 0.020 mg, together with one or more pharmaceutically acceptable carriers for at least 21 daily dose units.

2. Pharmaceutical product for oral contraception comprising 1.5 mg of dienogest and 0.015 mg or 0.020 mg of ethinylestradiol or 2.0 mg of dienogest and 0.015 mg of ethinylestradiol, together with one or more pharmaceutically acceptable carriers to form at least 21 daily dose units of a 28-day menstrual cycle.

3. Product according to Claim 2, where the pharmaceutical product is a film-coated tablet consisting of a tablet core with a dienogest content and of an active ingredient-containing film coating with a dienogest content and a total ethinylestradiol content.

4. Product according to either of Claims 2 to 3, where there is delayed dissolution of the proportion of dienogest of at least 30%, preferably 50%, of dienogest from the tablet core after more than 30 min, and dissolution of the proportion of dienogest and of the total ethinylestradiol content of at least 75% in a maximum of 45 min, preferably 70% in 30 min, from the film coating, as determined by the dissolution test using water at 37°C as dissolution medium and 50 rpm as stirring speed.

5. Product according to any of Claims 2 to 4, where the number of daily dose units comprising the combination of dienogest and ethinylestradiol amounts to 22, 23, 24 or 25, and the number of daily dose units containing no active ingredient amounts to 6, 5, 4 or 3.